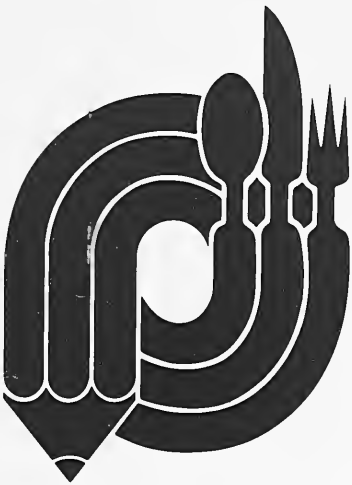
Annual Report of the
National Institutes of Health

PROGRAM IN BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING FISCAL YEAR 1983



NIH Nutrition
Coordinating Committee

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Annual Report of the
National Institutes of Health (U.S.)

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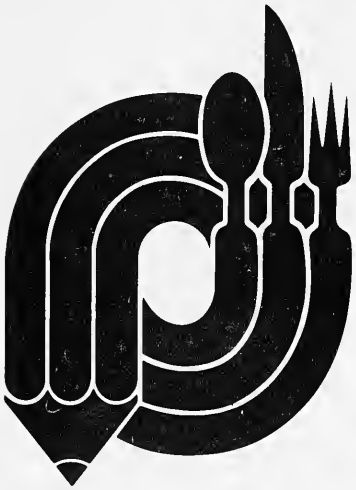

Prepared by
NIH Nutrition
Coordinating Committee

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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Chairman	Artemis P. Simopoulos, M.D.
Members and (Alternates)*	
National Cancer Institute	William DeWys, M.D. (Ritva Butrum, Ph.D.)
National Heart, Lung, and Blood Institute	Nancy Ernst (Basil M. Rifkind, M.D.)
National Institute of Dental Research	Sharon L. Johnson, Ph.D.
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*(Alternates in parenthesis)

As of September 30, 1983

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Cochairperson and Executive Secretary	Ms. Karen Donato Nutrition Coordinating Committee Office

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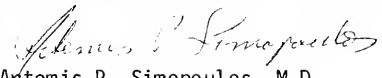
National Cancer Institute	Dr. Robert Hadsell
National Eye Institute	Dr. Barbara Underwood
National Heart, Lung, and Blood Institute	Ms. Marilyn Farrand
Office of Communications	Mr. Don Ralbovsky

ACKNOWLEDGEMENTS

I want to pay special thanks to the Institutes' representatives to the Nutrition Coordinating Committee whose unfaltering support and interest in nutrition research has made possible the development of the report. On behalf of the Nutrition Coordinating Committee I wish to thank three members of the NCC office staff: Ms. Karen Donato for her excellent work in updating the annual report; Dr. Thomas Vogl for the extensive analysis of the program based on the computerized data retrieval system; and Ms. Sherri Wisner for her editorial and technical assistance in the preparation of the report.



Artemis P. Simopoulos, M.D.
Chairman, Nutrition Coordinating Committee
Office of the Director
National Institutes of Health

PREFACE

The National Institutes of Health is the major agency in the Federal Government that supports research and training in nutrition as it relates to health maintenance, human development throughout the life cycle, disease prevention, and disease treatment. The NIH Program in Biomedical and Behavioral Nutrition Research and Training is supported by all 11 Institutes and one Division, namely:

NCI	-	National Cancer Institute
NHLBI	-	National Heart, Lung, and Blood Institute
NIDR	-	National Institute of Dental Research
NIADDK	-	National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
NINCDS	-	National Institute of Neurological and Communicative Disorders and Stroke
NIAID	-	National Institute of Allergy and Infectious Diseases
NIGMS	-	National Institute of General Medical Sciences
NICHD	-	National Institute of Child Health and Human Development
NEI	-	National Eye Institute
NIEHS	-	National Institute of Environmental Health Sciences
NIA	-	National Institute on Aging
DRR	-	Division of Research Resources

The Fogarty International Center (FIC) is included this year because of support in nutrition research; however, FIC does not support research on an annual basis.

Nutrition is an important, crosscutting program area within the NIH. For this reason, the nutrition program is coordinated through the NIH Nutrition Coordinating Committee (NCC) that operates out of the Office of the Director and is advisory to the Director. The membership of the NCC consists of representatives from the 11 Institutes and the Division that support nutrition research. Additional NIH offices and other agencies of the Department of Health and Human Services have liaison representatives to the committee.

The mandate of the Nutrition Coordinating Committee is to review, stimulate, and encourage the necessary support of nutrition research and training in order to better define the role of nutrition in the promotion of health, and the prevention and treatment of disease.

Each year, the NCC prepares the "Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training" for the preceding fiscal year and sponsors a major conference or workshop in nutrition that includes the interests of many Institutes.

The committee is the focus for the review of nutrition research and training priorities, their coordination, and for the development of the NIH Program in Biomedical and Behavioral Nutrition Research and Training. This focus minimizes duplication of effort among the Institutes and identifies areas where research, research training, and research manpower development in nutrition need to be advanced. This is accomplished through joint program announcements (PA's) and requests for applications (RFA's) developed by the committee and sponsored by more than one Institute. Committee representatives are also encouraged to have their individual Institutes develop program announcements, requests for applications, and requests for proposals (RFP's). In FY 1983, the Institutes continued to emphasize the nutrition research program through the publication in The NIH Guide for Grants and Contracts of six PA's, six RFA's, and seven RFP's.

The NIH nutrition program includes extramural and intramural research and research training, and research manpower development. The major component of the NIH nutrition program is the extramural research program carried out at various universities; in graduate science departments, principally departments of nutrition; and in medical, dental, and other health professional schools, especially schools of public health. The NIH intramural program in nutrition research is carried out on the NIH campus in Bethesda, Maryland, primarily at the Clinical Center, with the exception of the programs of two Institutes: The intramural program of the National Institute on Aging is carried out at the Gerontology Research Center in Baltimore, Maryland, while that of the National Institute of Environmental Health Sciences is located in Research Triangle Park, North Carolina.

The committee plays a key role in the development of nutrition policy at the NIH. Currently, nutrition policy at the NIH emphasizes eight critical areas. Research in four of these critical areas includes: clinical nutrition throughout the life cycle; the role of nutrition in disease development; prevention of disease; and treatment of disease. The other four critical areas include: transfer of modern nutrition technology; nutrition education for professionals and the public; nutrition research training and research manpower development in nutrition; and the coordination of all these activities.

Part I of this year's annual report presents the FY 1983 Program in Biomedical and Behavioral Nutrition Research and Training, beginning with the definition of nutrition research at the NIH and then focusing on the FY 1983 obligations for nutrition research and training. The analysis of the fiscal aspects of the program include an overview of the nutrition program and a comparison of actual obligations for nutrition with NIH obligations as a whole. For the first time this year, the expenditures of the NIH nutrition program are also analyzed according to the 34 classification categories of the Human Nutrition Research and Information Management System.

A description of the NIH Clinical Nutrition Research Units (CNRU's) program follows as well as selected highlights of the third annual meeting of the CNRU Directors, that was held in conjunction with the First Annual Conference of Federally-Supported Human Nutrition Research Units, sponsored by the JSHNR. Information pertinent to the extramural and intramural nutrition research programs is then presented by Institute, followed by a description of the nutrition research training program. Concluding Part I are nutrition research highlights of particular scientific interest and importance. The inclusion of nutrition research highlights appear for the first time in the report because the NCC feels very strongly that the nutrition program of the NIH under the leadership of the NCC has contributed extensively to the achievement of these research accomplishments.

Part II of the report describes the structure of the NIH Nutrition Coordinating Committee, the charge of the Subcommittee on Nutrition Education, and highlights of the committee's and subcommittee's activities and accomplishments in FY 1983. Two highlights of particular interest are the "Eat Well, Be Well II" videotape series, produced by Amram Nowak Associates with funds from the Metropolitan Life Insurance Foundation, in consultation with the NCC, and the development of the NIH-NCC Nutrition Research Exhibit.

Part III describes the major responsibilities and activities of the NCC office. These activities encompass: responding to information requests about nutrition in general and about the NIH nutrition program in particular from the Congress, other Federal agencies, the scientific community and the public; representing NIH in various nutrition activities under way at the Office of the Assistant Secretary for Health; and presenting the NIH Program in Nutrition at national and international meetings, conferences, and workshops. The development of the Human Nutrition Research and Information Management System is presented, followed by a description of the Departmental Research Initiative in Nutrition, and finally highlights of the work of the Joint Subcommittee on Human Nutrition Research (JSHNR) are given.

FY 1983 marked the establishment of the Federal Human Nutrition Research and Information Management (HNRIM) System, a computerized data base and information retrieval system that includes data on every federally supported nutrition research project. The NCC office staff, supported by the NIH Division of Computer Research and Technology (DCRT) and in collaboration with the United States Department of Agriculture (USDA), through the USDA-DHHS joint task force on HNRIM, under the auspices of the JSHNR and its successor the Interagency Committee on Human Nutrition Research, developed the HNRIM System. In December 1981, Congress mandated the Secretaries of DHHS and USDA to formulate a plan for the Human Nutrition Research and Information Management System. The plan was transmitted to Congress in July 1982. In FY 1983, the HNRIM Task Force prepared for Congress the first in a series of annual progress reports on the system; this report describes the development of the on-line data management system that provides access to over 3,800 nutrition research projects.

The DHHS Research Initiative in Nutrition (DRIN), coordinated by the NCC Chairman, continues to provide a focus for the coordination of nutrition research activities of the six agencies--NIH, ADAMHA, FDA, CDC, NCHS, and HRSA--that conduct or support nutrition research and training within the Department. Noteworthy this year is the development of the Department's 5-Year Plan for Human Nutrition Research and Training, by the six agencies of the DRIN, which will be included in the Federal 5-Year Plan for Human Nutrition Research and Training, being developed by the ICHNR. Because of the importance of the 5-Year Plan and the interest of the scientific community in the plan, the 5-year priorities in nutrition research and research training prepared by the NIH Institutes are included in the report as appendix F.

The NCC office continued to serve as the executive secretariat for the Joint Subcommittee on Human Nutrition Research, of the Committee on Health and Medicine and the Committee on Agriculture, Food, and Forestry Research of the Federal Coordinating Council for Science, Engineering and Technology, Office of Science and Technology Policy in the Executive Office of the President, until the termination of the JSHNR on June 10, 1983. The JSHNR was succeeded by the Interagency Committee on Human Nutrition Research (ICHNR), which is cochaired by the Assistant Secretary for Health, DHHS, and the Assistant Secretary of Agriculture, Science and Education, USDA, and has functions similar to the JSHNR. The NCC Chairman serves as the NIH representative to the ICHNR.

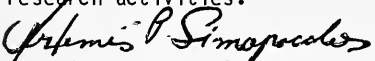
Part IV consists of six appendices: appendix A includes the mandate of the Nutrition Coordinating Committee; appendix B presents the nutrition policy of the NIH; appendix C presents the FY 1983 nutrition expenditures of the 11 Institutes, DRR, and FIC by support mechanism; appendix D presents the JSHNR definition of human nutrition research; appendix E includes the legislative authority of NIH for human nutrition research; and appendix F includes the NIH criteria for priority setting and planning for nutrition research and the 5-year priorities in nutrition research and research training by Institute.

During FY 1983, the Nutrition Coordinating Committee and the NCC office were very much involved in the implementation of, as well as the planning for, a number of national as well as international nutrition research activities that involved not only the NIH Institutes and Divisions, but also other PHS agencies, Federal agencies outside the DHHS, and professional societies. One activity of particular importance was planning for one of the six satellite meetings of the IV International Congress on Obesity, entitled "The Outpatient Management of Obesity: Standards and Methods of Assessment," held October 2-4, 1983, in Washington, D.C., which addressed the prognostic factors of obesity, assessment of motivation and compliance, integration of treatment modalities for obesity, and characteristics of professional weight control programs. The satellite workshop was sponsored by the NCC. Highlights of the satellite workshop were presented at the IV International Congress on Obesity, in New York City on October 5-8, 1983. Another important and timely nutrition conference for which the NCC planned for in FY

1983 involved the many aspects of the issues related to nutrition and hypertension. The NCC, NHLBI and the NIA cosponsored the conference, entitled "Nutrition and Hypertension," that took place March 12-14, 1984, in Bethesda, Maryland.

In the area of program development in nutrition research, in addition to the PA's, RFA's, and RFP's issued in FY 1983, a number of the Institutes began to plan for the publication of joint announcements in FY 1984. Of particular interest is the reissuing of the RFA on the Clinical Nutrition Research Units by NIADDK, NCI and NIA, to be published in August 1984. Obesity was another area of research identified by the NCC as important for future research. As a result, the NCC developed the joint PA entitled "Studies on Obesity" with the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA); six of the NIH Institutes joined forces with the three ADAMHA Institutes in order to address the many research questions related to the etiology, treatment and prevention of obesity. The PA was published in March 1984. Other plans are already in place for more program announcements and conferences to be sponsored by the Institutes and the NCC office.

These activities illustrate the great spirit of cooperation that has been developed among the PHS agencies, the NIH Institutes, and the professional societies both nationally and internationally. We look forward to next year with the anticipation of continued effective cooperation and collaboration that the NCC fosters for nutrition research activities.



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Chairman,
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I.

THE FY 1983 PROGRAM IN BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING

The Program in Biomedical and Behavioral Nutrition Research and Training is based on a common definition of nutrition research and a computerized data retrieval system that allows for an extensive analysis of the program's scientific content and its expenditures. The program is classified according to the 34 categories for nutrition research used by the Federal government-wide computerized Human Nutrition Research and Information Management (HNRIM) System and six special interest areas.

The nutrition research program is presented in terms of the financial obligations in nutrition by category of support; program descriptions by Institute; and in terms of highlights of nutrition research. The program continues to expand as a result of a number of requests for applications, requests for proposals and program announcements development by the Institutes themselves or jointly with the Nutrition Coordinating Committee, as well as the ever increasing interest of basic scientists and clinical investigators in the many aspects of nutrition research.

The NIH nutrition program is supported by the 11 Institutes, the Division of Research Resources, and the Fogarty International Center and is coordinated through the Nutrition Coordinating Committee. The program supports research and research training in nutrition as it relates to health maintenance, human development throughout the life cycle, disease prevention, and disease treatment.

DEFINITION OF NUTRITION RESEARCH AT THE NIH

Included in the first report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1977 issued by the NCC was the definition of biomedical and behavioral nutrition research that the NCC developed. That definition, which continues to serve as a basis for data retrieval and for the assessment of information about the nutrition research and training activities of the NIH, is as follows:

> "The term nutrition research includes studies designed to assess the consequences of food or nutrient intake and utilization in the intact organism, including man, and the metabolic and behavioral mechanisms involved. These studies encompass investigation of nutrient variables at the cellular or subcellular level. This definition also includes:
>
> - Research designed to elucidate the metabolic role or function of nutrients in both animal models and man.
> - All studies concerned with genetic-nutrient-environmental interactions where a nutrient is a variable.
> - Dietary studies expected to produce significant changes in health status, including the maintenance of health and the treatment of disease in man. Such studies might include clinical trials, epidemiological studies, metabolic studies, surveillance, and nutritional status monitoring studies."

FY 1983 OBLIGATIONS FOR NUTRITION RESEARCH AND TRAINING

Overview of the Nutrition Program

In FY 1983, the total NIH actual obligation in biomedical and behavioral nutrition research and training was $164,306,000. Actual obligations in nutrition by each Institute, DRR, and FIC are as follows:

NCI	$37,335,000	NICHD	$20,165,000
NHLBI	38,350,000	NEI	5,570,000
NIDR	2,071,000	NIEHS	1,390,000
NIADDK	33,332,000	NIA	4,391,000
NINCDS	2,547,000	DRR	15,444,000
NIAID	1,607,000	FIC	22,000
NIGMS	2,082,000		

To determine obligations for nutrition research and training, the Institutes' program staff reviews all research grants and contracts in order to identify the nutrition component of each project, in accordance with the definition of nutrition research, and then determines the percentage applicable to nutrition. The NIH has thus been able to eliminate such confusing and easily misunderstood terms as "primary/secondary," "major/minor," "nutrition related," and "direct/indirect" in referring to its nutrition program.

The analysis of the obligations of the NIH nutrition program is accomplished through the NCC office computerized data retrieval system that stores data on all the nutrition research and research training activities of the NIH. This data base is updated periodically and cross-checked against the NIH grant information and accounting system, IMPAC (Information for Management Planning, Analyses, and Coordination). This computer system has enabled the NCC office to carry out detailed analyses in terms of percentage of the nutrition component, support mechanism (contract, type of grant, etc.), and special interest area. Other analyses are performed on an ad hoc basis.

Up through FY 1982, the NIH nutrition program was presented in terms of 15 special interest areas. This year the program is presented in accordance with the classification used by the Human Nutrition Research and Information Management System. This system includes a data base and computerized data retrieval system that contains data on the nutrition research programs of the following Federal agencies: Department of Health and Human Services; U. S. Department of Agriculture; Veterans Administration; Agency for International Development; Department of Defense; and Department of Commerce-National Oceanic and Atmospheric Administration. The HNRIM classification system is presented in its entirety beginning on page 12. A narrative on the development of the HNRIM system can be found on pages 133-35.

Figure 1 presents the nutrition research and training obligations of each Institute and DRR. The total nutrition obligation by Institute is represented by a bar divided into five segments. The lowest segment of the bar represents those grants and contracts with a nutrition component less than 50 percent of the entire grant or contract, followed by those with a nutrition component of 50 to 99 percent, and then those that are entirely (100 percent) nutrition research. The fourth segment represents training grants and fellowships, and the fifth segment represents intramural research obligations.

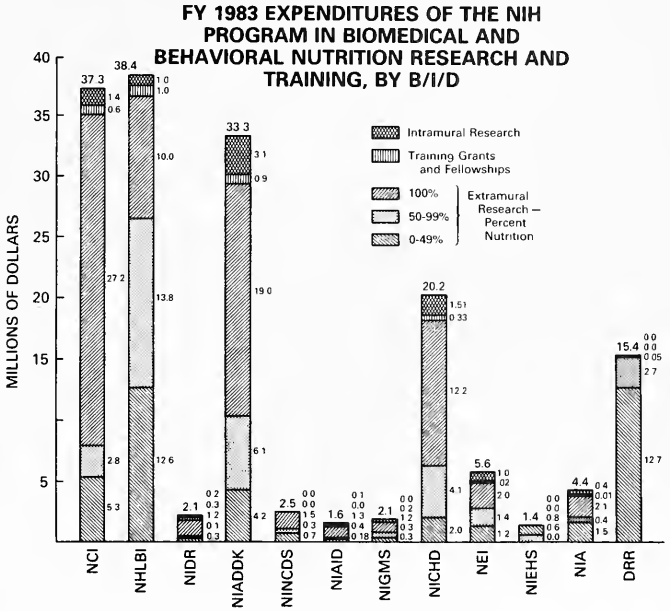
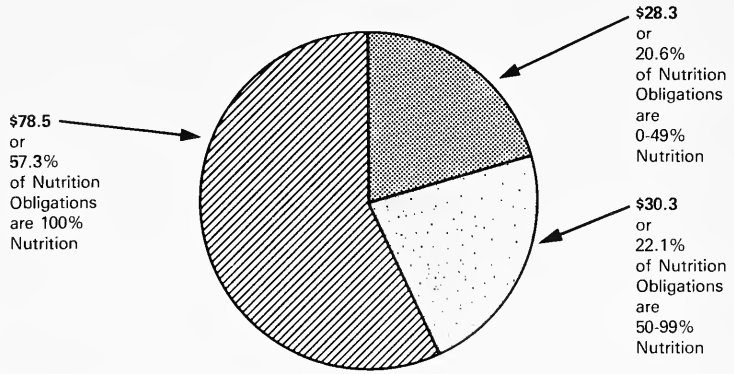


Figure 1

Figure 2 illustrates the extramural research support of the 11 Institutes, excluding DRR. About 60 percent of the funds are expended for projects that are entirely nutrition research; 20 percent are 50-99 percent nutrition; and the remaining 20 percent of the funds are projects with less than 50 percent nutrition research. Thus, the majority of the NIH program in nutrition research consists of projects where the investigators are carrying out research that is devoted entirely to nutrition.

Nutrition Obligations for all Grants and Contracts* Active in FY'83 by Percent of Nutrition Component

Dollars in Millions



*Excludes nutrition obligation for DRR and for training.

Figure 2

Table I presents the FY 1983 nutrition obligations by category of support for the NIH as a whole, and appendix C contains the obligations for each Institute, DRR, and FIC (Tables C-1 through C-13).

TABLE I

National Institutes of Health
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	1,204	78,749		
	Clinical trials	151	8,621		
	Total			1,355	87,370
Program projects:	Regular	76	16,701		
	Clinical trials	7	2,542		
	Total			83	19,243
Contracts:	Regular	78	9,057		
	Clinical trials	30	3,900		
	Total			108	12,957
Centers:	Regular	64	12,468		
	Clinical trials	2	9		
	Total			66	12,477
Research Resources Support				274	15,551
Reimbursement Agreements				15	955
Research Career Development Awards				57*	1,183
New Investigator Research Awards				73*	2,305
Training:	Training grants	377*	3,056		
	Fellowships	34*	391		
	Total			411*	3,447
Subtotal - Extramural					$ 155,488
Intramural					
Projects				91	8,134
Training				47*	684
Subtotal - Intramural					$ 8,818
TOTAL NUTRITION RESEARCH AND TRAINING - NIH					$ 164,306

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

The extramural program is classified by mechanism of support into regular research grants, program projects, contracts, and centers. Clinical trials are funded by all four of these mechanisms. Research resources support, reimbursement agreements, research career development awards, new investigator research awards, and training grants and fellowships are also included in the extramural program. The intramural program consists of research projects and training (fellowships). In FY 1983, the actual obligations for extramural research, training, and manpower development accounted for $155,488,000, while intramural research and training accounted for $8,818,000.

Research grants support a discrete, specified, circumscribed project performed by investigator(s) in areas representing specific interests and competencies. Such research is initiated entirely by investigators outside the NIH. In FY 1983, the NIH supported 1,355 research grants in nutrition for a total obligation of $87,370,000. This category constitutes the largest single area of support in nutrition.

Program projects are also investigator initiated research, but differ from research grants in that they are awarded for the support of a broadly based, multidisciplinary, often long-term research program that has a specific major objective or a basic theme. A program project generally involves the organized efforts of relatively large groups, members of which are conducting research projects designed to elucidate various aspects or components of the major objective. In FY 1983, 83 program projects in nutrition were funded for $19,243,000.

Contracts are initiated by the agency to develop or apply new knowledge or to test, screen, or evaluate a product, material, device, or component for use by the scientific community. In FY 1983, NIH funded 108 nutrition research contracts for $12,957,000.

Centers are an additional component of agency initiated research that support any part of a full range of research and development from very basic to clinical. Centers may involve ancillary supportive activities, such as protracted patient care necessary to the primary research effort. The spectrum of activities comprises a multidisciplinary approach to a specific disease entity or biomedical problem area. In FY 1983, NIH obligations for the 66 centers with nutrition research activities were $12,477,000.

Investigator initiated research (research grants and program projects) in FY 1983 amounted to $106,613,000 (or 65 percent of all nutrition research and training obligations) whereas agency initiated research support in nutrition (contracts and centers) was $25,434,000 (or 15 percent of nutrition research and training obligations). Thus direct support for nutrition research was predominantly investigator initiated.

Clinical trials in nutrition are supported by each of the four major mechanisms discussed above--research grants, program projects, contracts, and centers. A clinical trial is defined as a scientific research activity undertaken to define, prospectively, the effect and

value of prophylactic/diagnostic/therapeutic agents, devices, regimens, procedures, etc., applied to human subjects. The study must be prospective, and intervention of some sort must occur. The number of cases or patients depends on the hypothesis being tested, but must be sufficient to permit anticipation of a definite, statistically significant, result. Phase I, feasibility, or pilot studies are excluded by definition.

FY 1983 obligations in support of 190 clinical trials involving nutrition totaled $15,072,000. These obligations constitute 9 percent of total nutrition obligations for FY 1983. The distribution of clinical trials among the four support mechanisms is displayed in table II.

TABLE II

SUPPORT MECHANISMS FOR CLINICAL TRIALS, FY 1983
(in thousands of dollars)

Funding Mechanism	Number of Clinical Trials	FY 1983 Expenditures
Research Grants	151	8,621
Program Projects	7	2,542
Contracts	30	3,900
Centers	2	9
TOTAL	190	15,072

Research resources support is provided by the Division of Research Resources and NICHD. In FY 1983, $15,551,000 was devoted to this category of the NIH nutrition program, with DRR expending $15,444,000 through the following five mechanisms:

1. The General Clinical Research Centers Program, with nutrition obligations of $12,504,000 in FY 1983, constitutes the bulk of DRR general research support. These centers foster the development of technological and therapeutic advances to expedite the application of basic biological knowledge into effective patient care.

The balance of $2,940,000 is provided through the following four mechanisms:

2. The Animal Resources Program provides a unique institutional research environment for the use of nonhuman primates or other animals in multicategorical research.

3. The Biomedical Research Support Program responds to emerging research opportunities and allows the supported institution self-determination in the development and conduct of pilot and other small projects.

4. The Biomedical Research Technology Program attempts to interface the knowledge of the physical sciences, mathematics, and engineering with biology and medicine.

5. The Minority Biomedical Support Program provides funds to ethnic minority institutions to conduct research.

Reimbursement agreements are entered into between the NIH and other Federal agencies. In FY 1983, 15 such agreements were made in the area of nutrition by five Institutes, with total obligations of $955,000. The 15 reimbursement agreements are listed in table III.

Research Career Development Awards and New Investigator Research Awards further manpower development in nutrition research. In FY 1983, 10 Institutes supported 130 individuals at a total cost of $3,488,000 by these mechanisms.

Training in biomedical and behavioral research is supported by NIH through national research service awards. Training grants are awarded to institutions; fellowships are awarded to individuals. In FY 1983, 377 extramural trainees in nutrition research were supported for a total of $3,056,000, and 34 fellowships awarded for a total of $391,000. Thus, total support for extramural training was $3,447,000 for the 411 trainees and fellows. (See also table IX.)

Intramural nutrition research and training was carried out by eight Institutes with a total obligation of $8,818,000, of which $684,000 was devoted to training (fellowships) by three Institutes.

TABLE III

INTERAGENCY REIMBURSEMENT AGREEMENTS WITH NUTRITION RESEARCH COMPONENTS FUNDED BY NIH IN FY 1983

NCI	- Followup of the National Health and Nutrition Examination Survey (NHANES) (with National Center for Health Statistics)
	- NHANES I Epidemiologic Followup Survey/Chemoprevention (with National Center for Health Statistics)
	- Chemoprevention of Epithelial Cancer by Retinoids (with Department of Energy at Brookhaven National Laboratory)
	- Research on Occupational Carcinogenesis (with National Institute of Occupational Safety and Health)
	- Epidemiological Studies of Cancer in Alaskan Natives (with Centers for Disease Control)
	- Procurement of Human Tissues (with U.S. Naval Medical Command)
	- Knowledge, Attitudes and Behaviors Related To Cancer (with Food and Drug Administration)
NHLBI	- Atherosclerosis Project--Nonhuman Primates (with DRS)
	- CDC-NHLBI HDLC Standardization Program (with Centers for Disease Control)
	- CDC-NHLBI International Lipid Research Clinics (with Centers for Disease Control)
	- CDC Lipid Standardization Program (with Centers for Disease Control)
	- Services Provided To NHLBI for Nutrient Composition Lab (with U.S. Agricultural Research Center)
NIA	- Followup Study of National Health and Nutrition Examination Survey Respondents (with National Center for Health Statistics)
NIAID	- Support of National Health and Nutrition Examination Survey (with National Center for Health Statistics)
NICHD	- Contraceptive Steroid Use from NHANES (with National Center for Health Statistics)

Comparison of Nutrition Program With Overall NIH Program

The entire NIH appropriation for FY 1983 was $4,023,969,000 and the nutrition obligation was $164,306,000. Thus, nutrition accounts for 4.1 percent of the total NIH budget. The nutrition component of all NIH research grants and program projects was 5.1 percent, of contracts 4 percent, and of centers 3.3 percent. Research grants and program projects (investigator initiated research) constitute the major part of NIH support. As can be seen from table IV, research grants and program projects account for 75 percent of the NIH extramural research component and 81 percent of the nutrition budget. Contracts represent 12 percent for NIH and 10 percent of the nutrition program, while centers represent 13 percent for NIH as a whole and 9 percent for the nutrition program. The data indicate that with respect to contracts and centers, the nutrition program lags behind NIH programs as a whole.

TABLE IV

COMPARISON OF TOTAL NIH AND NUTRITION OBLIGATIONS IN THE THREE MAJOR COMPONENTS OF EXTRAMURAL RESEARCH, FY 1983
(in thousands of dollars)

	NIH Total		Nutrition Program	
Research grants and program projects	2,095,116	(75%)	106,613	(81%)
Contracts	320,090	(12%)	12,957	(10%)
Centers	373,369	(13%)	12,477	(9%)
TOTAL (of the three components)	2,788,575	(100%)	132,047	(100%)

Human Nutrition Research and Information Management Classification System

The classification categories used by the HNRIM system were originally developed by the Joint Subcommittee on Human Nutrition Research to reflect all the components included in the JSHNR definition of human nutrition research (appendix D) that was accepted by all the concerned Federal agencies in 1980. Nutrition projects included in the system are classified under five major areas: I. Research in the Biomedical and Behavioral Sciences; II. Research in Food Sciences; III. Research on Nutrition Monitoring and Surveillance of Populations; IV. Research in Nutrition Education; and V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition. Research in the Biomedical and Behavioral Sciences is subclassified under three major components: A. Research on Normal Nutritional Requirements Throughout the Life

Cycle; B. Diseases and Conditions; and C. Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels. The system is subsequently divided into 34 categories. Each nutrition research project is assigned at least one of the 34 classifications, and as many classifications as are needed are chosen in order to adequately identify all major nutrition aspects of the research activity being classified. The HNRIM classification system is presented below.

HNRIM Classification System

I. Research in the Biomedical and Behavioral Sciences

A. Research on Normal Nutritional Requirements Throughout the Life Cycle

The following five categories are included because of the importance to health promotion of establishing normal nutritional requirements throughout the life cycle, and the differing needs of individuals at various stages of the life cycle.

Research activities relevant to normal nutrition at specific stages of the human life cycle should be assigned to classifications 1-5.

1. Maternal Nutrition

2. Infant and Child Nutrition (0-12 years)
   (includes the low birth weight infant)

3. Adolescent Nutrition (13-18 years)

4. Adult Nutrition (19-65 years)

5. Nutrition of the Elderly (65+ years)

B. Diseases and Conditions

Research on the role of nutrition in the prevention, amelioration, and treatment of diseases and conditions should be assigned to categories 6-16.

6. Cardiovascular Disease and Nutrition

7. Cancer and Nutrition

8. Other Diseases and Nutrition
   (e.g., osteoporosis, diabetes, etc.)

9. Trauma (Including Burns) and Nutrition

10. Infection--Immunology and Nutrition

11. Obesity, Anorexia, and Appetite Control

12. Genetics and Nutrition

13. Nutrition and Function
    (Includes mental, psychomotor, and work performance; environmental stress)

14. Nutrient Interactions
    (Includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)

15. Other Conditions and Nutrition

16. Nutritional Status
    (Includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

C. Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels

Categories 17-25, 14, and 27 classify research by nutrient variables; these categories should be used to indicate the nutrient variables in research classified elsewhere; and classify biochemical, subcellular, cellular, and animal research, such as studies of nutrient mechanisms and metabolism not related to specific diseases, conditions, or stages of the life cycle.

17. Carbohydrates

18. Lipids (Fats and Oils)
    (Includes essential fatty acids, lipo- and apoproteins)

19. Alcohols
    (Includes ethanol, sorbitols, and other alcohols used as components in synthetic and semisynthetic foods)

20. Proteins and Amino Acids
    (Includes essential as well as nonessential amino acids such as taurine and carnitine)

21. Vitamins
    (Includes vitamin A, C, B_6, B_{12}, D, E, K, thiamin, riboflavin, niacin, folacin, biotin, and pantothenic acid)

22. Minerals and Essential Trace Elements
    (Includes calcium, phosphorus, magnesium, iron, zinc, iodine, copper, manganese, fluoride, chromium, selenium, and molybdenum)

23. Water and Electrolytes
(Includes sodium, potassium, and chloride)

24. Fiber

25. Other Nutrients In Food
(Such as cobalt, nickel, vanadium, silicon, tin, arsenic, cadmium, choline, lecithin and various growth factors)

*14. Nutrient Interactions
(Includes nutrient-nutrient interactions, nutrient-drug interactions, nutrient-toxicant interactions, and nutrient toxicity)

*27. Bioavailability of Nutrients
(Includes methods for the determination of bioavailability of nutrients)

II. Research in Food Sciences

Categories 26-29 should be used for research in the nutritional aspects of food sciences.

26. Food Composition
(Includes nutritional quality, nutrient content, and research on methods of analysis for nutrients and fiber)

27. Bioavailability of Nutrients
(Includes methods for the determination of bioavailability of nutrients)

28. Effects of Technology on Acceptability and Nutritional Characteristics of Foods and Diets
(Includes the beneficial and adverse effects of varietal and species differences, harvest and post-harvest technology, retail food practices, food processing, handling, preservation, and home cooking.)

29. Other Research in Food Sciences

III. Research on Nutrition Monitoring and Surveillance of Populations

30. Food Consumption Surveys
(Includes research on methods for determination of food consumption and its trends, and research utilizing data derived from such surveys.)

31. Studies of Dietary Practices, Food Consumption Patterns, and Their Determinants.

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* This category is listed here to indicate that it may also be applicable to research on Nutrient Metabolism and Metabolic Mechanisms at the Cellular and Subcellular Levels (Class I.C).

**16. Nutritional Status
(Includes research on methods for the determination of nutritional status and surveillance: dietary history and food consumption, biochemical determinants, anthropometry, and clinical examination)

IV. Research in Nutrition Education

Categories 32-33 encompass research in nutrition education.

32. Studies on Methods for Informing and Educating the Public About Nutrition, Health, and Dietary Practices and for Countering Nutrition Misinformation
(Includes studies on methods for informing and educating professionals in these areas.)

33. Other Research in Nutrition Education

V. Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition

34. Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition.

Table V indicates the research support in the 34 HNRIM classification categories along with the number of grants and contracts. The column labeled 'percent of total' represents the funds expended in a given category in relation to total expenditures for nutrition research and research training, which for FY 1983 amounted to $164,306,000. It should be pointed out that a grant or contract may appear in more than one category. For example, a project on maternal PKU may appear under maternal nutrition and under genetics. Thus, the total expenditures in the 34 categories are larger than the sum of $164,306,000. It should be noted that while NIH nutrition research encompasses all 34 classification categories, by far the largest component of NIH nutrition research is concentrated in area I, Research in the Biomedical and Behavioral Sciences.

In addition to the 34 HNRIM categories, there are six areas of particular scientific or political interest to NIH. These six "Special Interest Areas" are: nutrition and prevention of disease, total parenteral and enteral nutrition, epidemiological research in nutrition, international nutrition research, nutrition education for the public, and nutrition education for professionals. The number of grants and contracts, the FY 1983 expenditures for these grants and contracts, and the percentage that these expenditures are of the total NIH nutrition program are displayed in table VI.

** This category is listed here because it may also be applicable to Nutrition Monitoring and Surveillance of Populations.

TABLE V

FY 1983 NIH EXPENDITURES
IN THE 34 HNRIM CLASSIFICATION CATEGORIES

Nutrition Research Classification Code	Area	Number of Grants and Contracts	Expenditure* (in thousands of dollars)	Percent of Total**
I.	Research in the Biomedical and Behavioral Sciences			
1.	Maternal Nutrition	98	8,491	5
2.	Infant and Child Nutr.	325	31,302	19
3.	Adolescent Nutrition	33	6,035	4
4.	Adult Nutrition	28	2,140	1
5.	Nutr. of the Elderly	109	9,806	6
6.	Cardiovascular Disease and Nutrition	293	42,881	26
7.	Cancer and Nutrition	694	40,398	25
8.	Other Diseases and Nutr.	245	21,777	13
9.	Trauma (Burns) and Nutr.	33	2,149	1
10.	Infection, Immunology, and Nutrition	148	7,710	5
11.	Obesity, Anorexia, and Appetite Control	235	24,652	15
12.	Genetics and Nutrition	256	28,258	17
13.	Nutrition and Function	311	36,328	22
14.	Nutrient-Nutrient/Drug/ Toxicant Interactions	315	23,532	14
15.	Other Conditions & Nutr.	41	4,883	3
16.	Res. on Nutr. Status	302	30,871	19
17.	Carbohydrates	100	9,893	6
18.	Lipids (Fats and Oils)	331	43,182	26

(Table V continued)

Nutrition Research Classification Code	Area	Number of Grants and Contracts	Expenditure*	Percent of Total**
19.	Alcohols	32	3,385	2
20.	Proteins and Amino Acids	232	17,322	11
21.	Vitamins	417	40,129	24
22.	Minerals & Trace Elements	213	16,477	10
23.	Water and Electrolytes	96	13,617	8
24.	Fiber	25	5,032	3
25.	Other Nutrients in Food	17	1,512	1
26.	Food Composition	34	3,154	2
27.	Bioavailability	48	3,727	2
II.	Research in Food Sciences			
28.	Effects of Technology on Foods and Diets	13	446	<1
29.	Other Res. In Food Sci.	10	334	<1
III.	Research on Nutrition Monitoring & Surveillance of Populations			
30.	Food Consumption Surveys, R&D	23	1,588	1
31.	Research on Dietary Practices, Food Consumpt., etc.	57	9,067	6
IV.	Research in Nutrition Education			
32.	Methods for Educating & Informing the Public	77	11,690	7
33.	Other Research in Nutr. Ed.	9	329	<1
V.	Research on the Effects of Government Policy and Socioeconomic Factors on Food Consumption and Human Nutrition			
34.	Effects of Govt. Policy & Socioeconomic Factors	2	50	<1

*A grant or contract may be assigned to more than one of these areas.

**The total expenditure of the NIH nutrition program in FY 1983 was $164,306,000.

TABLE VI

NIH EXPENDITURES IN SPECIAL INTEREST AREAS
IN NUTRITION RESEARCH AND EDUCATION

Special Interest Area	No. of Grants or Contracts*	Expenditure* (in thousands of dollars)	Percent of Total**
SI-1. Prevention of Disease	1161	104,781	64
SI-2. Total Parenteral and Enteral Nutrition	75	7,268	4
SI-3. Epidemiological Research	176	26,411	16
SI-4. International Research	37	4,245	3
SI-5. Education for the Public	16	6,273	4
SI-6. Educ. for Professionals	68	5,316	3

*A grant or contract may be assigned to more than one of these areas.
**The total expenditure of the NIH nutrition program in FY 1983 was $164,306,000.

THE CLINICAL NUTRITION RESEARCH UNITS

The concept of the Clinical Nutrition Research Unit (CNRU) has been one of the most important accomplishments of the NCC. The CNRU's formed the basis of a new National Program in Clinical Nutrition Research. The RFA entitled "Core Grants for Clinical Nutrition Research Units (CNRU's)," published jointly by NCI, NIADDK, and NIA in January 1979, led to funding of four units in FY 1979 and three additional units in FY 1980. These seven CNRU's, which continued to receive support in FY 1983, are designed to provide the milieu for research, training, and education through coordinated effort, intellectual stimulation, and the use of shared resources.

The CNRU program, now in its fourth year, has been very successful in strengthening a multidisciplinary research program in clinical nutrition and in improving the educational program for medical students as well as other health professionals. In addition, the CNRU program has provided support for the training of new clinical investigators and the development of nutrition education materials for patients and the general public.

A CNRU is an integrated array of research, educational, and service activities that is oriented toward human nutrition in health and disease. It serves as the focal point for clinical nutrition research activities and for the stimulation of high quality research in areas such as improved nutritional support of acutely and chroni-

cally ill persons, nutritional support of the hospitalized patient, assessment of nutritional status, effects of disease states on nutritional needs, and effects of changes in nutritional status on disease. Each CNRU must consist of the following seven components: research with human subjects and populations; laboratory investigations; research training; shared facilities and research services; education programs for medical students, house staff, practicing physicians, and paramedical personnel; nutritional support services; and public information activities.

In order to foster integration and support interactions among the seven CNRU's, NIH sponsors an annual meeting of the CNRU Directors to discuss research progress and future research needs. The third annual meeting was held on December 15, 1982, and focused on improving communication between the CNRU's regarding ongoing research efforts. To explore a mechanism to meet this need, a computerized data retrieval system, based on the classification system of the Joint Subcommittee on Human Nutrition Research, and developed under NCI sponsorship, was demonstrated. This system is designed to assist the CNRU researchers to identify counterparts at other CNRU's with common research interests. The system contains information on all subprojects within each CNRU, categorized by the JSHNR classification system and by a key word index using the vocabulary of the National Library of Medicine's Medical Subject Heading (MESH). The CNRU directors unanimously approved the system and its classification and coding terms and expressed their desire to use the system when data entry has been completed for the final group of subprojects.

Following the CNRU's Directors' meeting, the first Annual Conference of Federally-Supported Human Nutrition Research Units, sponsored by the JSHNR, was held on December 16-17, 1982. The seven CNRU Directors presented highlights of the nutrition research under way at their respective units. This conference is described on pages 138-39 of this report.

In all of the CNRU's, nutrition is now being effectively integrated as a component of a broad spectrum of research projects that study the nutritional requirements throughout the life cycle and investigate the role of nutrition in cancer, cardiovascular diseases, diabetes, renal diseases, cystic fibrosis, digestive diseases, and osteoporosis, as well as in the management of patients with serious illness or injury. The CNRU's have begun to collaborate on joint research projects, on laboratory methods and services to standardize assays in order to obtain comparable results, and on education and outreach activities in order to increase the role of the CNRU's in nutrition education nationwide.

Each CNRU has made a commitment to provide training experiences in clinical nutrition for health professionals and young investigators at various levels. The presence of CNRU's at participating institutions has strengthened and enhanced nutrition education of both health professionals and the general public. Curriculum development in medical schools includes required and/or elective courses in basic

and advanced principles of nutrition sciences, independent study courses, special lectures, and preceptorships. The CNRU staffs also organize workshops and seminars, write and edit newsletters and pamphlets, and produce audiovisual and other kinds of informational materials in order to disseminate nutrition findings to physicians, other health professionals and lay persons in the community.

One of the important aspects of the CNRU's has been the increased visibility to nutrition programs, including opportunities for participation by medical students and fellows in research projects on nutrition problems, as well as the increased awareness of faculty of the appropriateness of a place for nutrition in the management of patients.

Because of the success of the CNRU program, the RFA was reissued to expand the program. NCI, NIADDK and NIA again participated in the revised RFA entitled "Core Grants for Clinical Nutrition Research Units," which will be published in the NIH Guide for Grants and Contracts in August 1984.

THE EXTRAMURAL RESEARCH PROGRAM

The major component of the NIH nutrition program is the extramural research program carried out at various universities; in graduate science departments, principally departments of nutrition; and in medical, dental, and other health professional schools, especially schools of public health. The extramural program is described under three major categories: the research program, manpower development, and program development.

The Research Program

Nutrition research supported by NIH includes the effects of nutrients on human growth and development, health maintenance and promotion, disease prevention, and disease treatment. The primary nutrition mission of NIH lies in biomedical and behavioral research and training. In addition, NIH funds nutrition education for professionals and the public as an integral part of many research programs and provides the public with nutrition pamphlets, public service announcements on radio and television, and materials for magazine articles. Nutrition education for professionals is provided through various scientific publications, conferences, and workshops. Appendix E describes the Institutes' legislative authorities for nutrition research.

NCI, NHLBI, NIDR, NIADDK, NINCDS, NIAID, NIGMS, NICHD, NEI, NIEHS, NIA, and DRR support research on requirements and basic metabolism of nutrients, the assessment of nutritional status of patients and populations, and the role of nutrition in health promotion and disease prevention. The following is a brief overview of the extramural activities of these Institutes.

The National Cancer Institute supports studies on the role of specific nutrients, both nutrient deficiencies and excesses, as well as of overall nutritional status on the initiation and promotion of cancer in the hope of discovering clues to aid in the prevention, and treatment or regression of the disease. Projects in cancer etiology, biology, diagnosis, prevention, and treatment are carried out in hospitals, research centers, and universities within the United States and abroad.

Studies examine the relationship of various dietary components on the mechanisms of carcinogenesis, i.e., promotional phases of neoplastic cell evolution and growth, carcinogen sequestration in the gastrointestinal tract, and immunocompetence capacity as related to carcinogen exposure and subsequent neoplastic cell growth. The nutrients being studied for their anticarcinogenic properties include vitamins A, E, K, C, B_6, and folic acid as well as zinc, copper, magnesium, and selenium.

Basic research is under way to examine the mechanisms by which vitamin A and its synthetic analogs inhibit the growth of leukemic cells, as well as the interactions of retinoids and vitamin A with the hormones essential to mammary gland differentiation. Other studies examine the effectiveness of retinoids as chemotherapeutic agents, e.g., topical application of retinoids on cervical mucosa is being examined, as well as the use of 13-cis-retinoic acid for the treatment of patients with familiar polyposis coli. Investigators are also examining the metabolism of vitamin B_6 during hepatocarcinogenesis in order to determine how hepatomas utilize and obtain pyridoxal phosphate; the uptake of ceruloplasmin copper in normal and tumor cells; the effects of selenium in the inhibition of pancreatic cancer of hamsters; the cocarcinogenic effect of choline deficient diets on the induction of liver tumors by several carcinogens; and the influence of vitamin C on the incidence, rate of progression of severity and mortality from mammary carcinoma.

Other studies examine the interaction of the various nutrients in terms of their role in carcinogenesis. For example, studies are under way on the role of vitamin C alone, as well as in combination with vitamin E (alpha-tocopherol), in the inhibition of carcinogenesis in patients at high risk of multiple basal cell carcinoma; the effects of vitamin E on the regulation of systemic vitamin A levels, i.e., the mechanisms by which vitamin E modulates the conversion of beta-carotene to vitamin A and its subsequent effects on carcinogenesis; the interactions of vitamins C, A, and E, zinc, selenium and protease inhibitors in terms of their roles as inhibitors of breast cancer; and the relationship of deficiencies of zinc, copper, and magnesium on the synthesis of "helper" factors, interleukin I and interleukin II, both of which are required for cytotoxic T lymphocytes.

The relationship of an individual's intake of fat, fiber, alcohol, and caffeine, as well as specific food additives such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) to carcinogenesis is also being investigated. Studies on breast cancer are

under way to examine the role of a high fat diet and whether a high protein/high fat diet has a synergistic effect on the initiation of mammary gland tumors. Determining whether these dietary excesses influence tumorigenesis through a neurohormonal mechanism is a major consideration. One study is examining the effects of long-term ingestion of a high fat diet on serum prolactin levels and on induced spontaneous mammary tumors in rats, while another study is looking at the effects of a low fat and high fiber intake on estrogen levels that may reduce the frequency of breast cancer.

Basic studies examine the role of specific fatty acids and cholesterol in the production of changes in the cell membrane and neoplastic transformations, as well as how alterations in the fatty acids in cell membranes increases the cell's susceptibility to chemotherapy and immunotherapy. Other investigators examine the role of varying dietary levels of fats, fats of various origins, and the degree of lipid saturation on the induction of skin cancer by ultraviolet light. In studies on the relation of fiber to the development of colon cancer, wheat bran, oat bran, guar gum and pectin are being studied in terms of their role in the production of changes in cell proliferation and kinetics, fecal pH, bile acid production, and the rates of intestinal tumor growth. Studies on the induction of esophageal cancers in rats examine the conversion of nitrates in food and water to nitrites and their reaction, particularly the iron III macrocyclic nitrate complexes with amines to form nitrosamines.

Studies continue to explore the question of whether dietary components serve as risk factors apart from other environmental factors in the etiology of various site specific cancers. A number of epidemiological case control studies focus on the relationships of the various dietary components to cancer of the bladder, colon, lung, pancreas, stomach, breast, skin, esophagus, and oral cavity. Tumor registry data are also being used to address these possible relationships. For example, a case control study is under way to test the hypothesis that low levels of selenium increases the risk of cancer of the breast, lung, and large bowel as well as to examine the relationship of selenium intake to tissue levels and the incidence of cancer. Another study is testing the hypothesis that increased plasma levels of beta-carotene, alpha-tocopherol and retinol, and increased levels of selenium in red cells reduces the risk of malignant melanoma. One study is examining the relationship between the dietary intake of vitamins A and E to serum levels in individuals who developed colon cancer while another is investigating the serum levels of vitamins A and E, selenium, and cholesterol in relation to lung cancer risk. Data collected from the Multiple Risk Factor Intervention Trial supported by NHLBI are also being used to study the relationship between dietary vitamin A and beta-carotene with serum levels of retinol and beta-carotene and subsequent cancer deaths in this population.

Other epidemiological research studies are under way to examine the incidence of cancer in relation to specific lifestyles and dietary habits of various populations such as the Seventh Day Adventists who consume a high fiber, low fat, lacto-ovo vegetarian diet without

caffeinated beverages or highly refined or spicy foods. The role of diet in cancer etiology is also being examined in three different populations: the multi-ethnic population of Hawaii, especially the Japanese living in Oahu; persons living in Utah; and in asbestos workers. In the group of asbestos workers, investigators are determining serum levels of vitamin A and beta-carotene in order to examine whether the likelihood of dying from lung cancer is related to preexisting serum levels of these substances.

Another hypothesis being tested is that exposure to cigarette smoke results in a localized vitamin B_{12} and folate deficiency limited to the bronchial epithelium, which renders it more susceptible to neoplastic transformation by the carcinogenic hydrocarbons of tobacco smoke.

Additional epidemiological studies evaluate the relative carcinogenicity of various alcoholic beverages comparing clear liquors (vodka, gin, light rum) which have few contaminants or congeners with alcoholic beverages such as beer and red and white wine. Positive epidemiological associations have been reported between consumption of alcoholic beverages, particularly beer, and large bowel carcinoma, the most common cancer in the U.S. Beer and ethanol consumption is thought to increase large bowel carcinogenesis by increasing fecal levels of bile acids and neutral sterols that are known promoters of colon carcinogenesis. Another study is examining the mechanisms by which alcohol increases the risk of cancers of the larynx, esophagus, and oral cavity in order to determine if dietary deficiencies of vitamins A and C, zinc, iron, and other nutrients increase the risk of neoplasms.

Other studies are under way to examine the reliability of dietary recall questionnaires, dietary history questionnaires, and interview methods used to assess food intake in epidemiological studies of cancer in various populations. Such studies will provide insight on the value of using a dietary questionnaire to obtain data today concerning dietary and alcohol intake for prior years (i.e., 5 to 30 years prior to the development of cancer).

The development of methods and tools for the nutritional assessment of cancer patients is important for understanding the effect of nutritional support on tumor response, tolerance to chemotherapy, performance status, and overall survival. Indirect calorimetry measures have revealed elevated basal metabolic rates for lean body mass in cancer patients. Malnourished cancer patients appear to be deficient in anabolic hormones, have excessive amounts of anti-insulin hormones and inappropriately elevated triiodothyronine levels. Information on limb fat, muscle and bone volume now available from computerized tomography (CT) is an important part of the evaluation and management of malignancy in various nutritional states.

In order to provide the proper nutritional support to the cancer patient, studies are under way on the abnormalities of glucose and lactate metabolism, the increased basal metabolic rates, and the overall nutritional status of the cancer patient. These studies

examine how nutritional support given during chemotherapy affects tumor response and patient survival by evaluating the effectiveness of parenteral and enteral nutrition in preventing or reversing the protein calorie malnutrition, maintaining or restoring immune competence, preventing treatment delays and improving tumor response. Other studies evaluate the effects of preoperative intravenous hyperalimentation on tumor growth parameters as measured by cell kinetics, as well as the use of various amounts of dietary protein as a method of reducing renal damage caused by radiation. Evaluation of nutritional support procedures and related social and behavioral changes as they apply to the prevention and treatment of anorexia, malnutrition, and cachexia in cancer patients is also under way. For example, one study examines the development of learned food aversions in patients with colon cancer receiving chemotherapy.

Research in genetics supported by NCI involves in vivo and in vitro observations of aflatoxin metabolism, the manipulation of amino acids, and the development of methods to discriminate markers specific to the cancer-prone genotype. The use of human cells to test and predict cancer risks has important implications for the identification of high risk patients in the general asymptomatic populations.

The NCI also supports two Clinical Nutrition Research Units, one at the University of Alabama in Birmingham and the other at the Memorial Sloan-Kettering Cancer Center. Basic nutrition research under way at these units includes studies on the effect of malnutrition on immune mechanisms, the relationships between zinc deficiency and immunological function, the requirements for folic acid coenzymes in purine biosynthesis, the use of oral and tube feedings of head and neck patients undergoing radiation therapy, and the selenium requirements of patients on parenteral nutrition.

The National Heart, Lung, and Blood Institute supports nutrition research in three major disease areas: heart and vascular diseases, blood diseases, and pulmonary diseases. A major portion of this research involves the role of nutrition in hypertension, atherosclerosis, and coronary heart disease. The role of nutrition in sickle cell disease, respiratory disease syndrome, and pulmonary function are also being investigated. The nutritional aspects of heart, lung, and blood diseases are supported across the biomedical research spectrum in basic research, applied research, clinical investigations, clinical trials, demonstration and education programs and research training.

Short-term investigations and epidemiologic studies suggest that fish oils contain fatty acids which may be metabolically unique and may be anti-atherogenic. Diets rich in omega-3-fatty acids have lipid lowering activity promoting lower levels of plasma cholesterol, low density lipoproteins, triglycerides and very low density lipoproteins. The omega-3-fatty acids are also associated with increases in bleeding time and decreases in platelet aggregation. Current research support includes studies in both humans and animal models. The further definition of the effects of omega-3-fatty acids is being investigated in animal models. The human nutrition research studies

of dietary omega-3-fatty acids include the following areas: mechanisms of the hypolipidemia effects; the efficacy and possible toxicity; and platelet and prostaglandin effects.

Several activities in cardiovascular/nutrition research are aimed at clarifying the role of dietary components in altering the atherosclerotic process. Basic research studies consider the effect of diet and heredity on the structure and function of lipoproteins; on the metabolism of lipids, lipoproteins and apolipoproteins as well as the progression and regression of the atherosclerotic plaque process; and on the relationship of abnormal carbohydrate metabolism to endogenous hypertriglyceridemia. Specific mechanisms for the control of cholesterol synthesis by the liver are under investigation, i.e., the possible role of hormones, cholesterol, cholesterol esters and other cholesterol metabolites are being evaluated in terms of their effect on the rate of cholesterol synthesis by the liver.

Other studies consider the role of trace elements in cardiac and pulmonary diseases. For example, copper deficiency in the rat has been found to result in pulmonary emphysema and cardiac hypertrophy, purpura, and neuropathology simulating Parkinson's disease while zinc deficiency results in platelet aggregation, hypotension, blood loss, water imbalance and glucose intolerance. Researchers are also investigating the mechanisms which increase blood flow to the digestive organs after a meal, while maintaining blood flow unchanged to the heart and kidney and reducing blood flow to the skin and muscles. These studies attempt to elucidate the role of nutrient absorption, intestinal nerves, and locally released chemicals and hormones in the control of these processes.

Community health education demonstration and intervention projects apply much of the knowledge gained from the epidemiological and basic research studies, and examine the effect of nutrition education on changes in dietary habits and the subsequent prevention or modification of cardiovascular disease risks. For example, nutrition intervention studies under way in the workplace, in clinical practice, and in school systems investigate the role of suggested dietary changes in lowering blood cholesterol, low density lipoproteins, triglycerides, and blood pressure. These changes in risk factors are then considered in terms of the possible prevention and control of hyperlipidemia, atherosclerosis, and hypertension. Research continues on the development of appropriate nutrition education programs and adherence strategies that help to reduce the diet-related risk factors for hypertension, obesity, and cardiovascular disease.

Dietary intervention studies attempt to determine the success of controlling blood pressure by nonpharmacologic means such as through weight loss and decreased sodium intake; to assess changes in peripheral vascular resistance in response to dietary potassium and sodium, such as the increased resistance with sodium in the hypertensive individual; to understand the relationships of dietary sodium and potassium to urinary prostaglandin excretion in terms of the etiology of hypertension; to examine renal humoral agents and the renal handling of sodium; and to develop quantitative methods for estimat-

ing sodium intake by measuring the excretion of sodium.

Research on nutrition's role in sickle cell disease and in thrombosis receives support from the Division of Blood Diseases and Resources. Research on sickle cell disease aims to define the effect of various nutrients on red cell physiology, as well as the contributions of vitamin and mineral deficiencies to growth retardation and immunologic function in patients with the disease. Studies on thrombosis and hemostasis investigate the role of dietary lipids on platelet structure and function. Another study investigates the role of vitamin E on platelet aggregation and fluidity of the platelet membrane.

Respiratory distress syndrome (RDS) is the single most frequent cause of death during the neonatal period. Research in this area, a priority of the Division of Lung Diseases, includes studies on maternal nutritional status as a means of reducing the risk of premature birth and subsequent risk of RDS. Two new binding proteins, one for retinol vitamin A and one for retinoic vitamin A, are being examined during perinatal development in terms of their role in the maturation of lung tissue. In addition, investigators are considering the influence of nutrition on lung defense functions such as the pulmonary alveolar macrophage and lung antioxidant enzymes. Since individuals with chronic obstructive lung disease are often malnourished, studies are under way to explain how malnutrition influences resistance to pulmonary infections, respiratory muscle fatigue, and lung surfactant function. In addition, vitamin C is being studied in terms of its role in the prevention of broncho-constriction in patients with asthma and bronchitis.

The National Institute of Dental Research supports research on the relationship between diet and nutrition, and the development and maintenance of both hard and soft tissues of the oral-facial complex. Special interests are in the problems of tooth and gingiva development and maintenance, periodontal diseases, and dental caries. NIDR's National Caries Program focuses on the development of a measure of the cariogenicity of various foods; the relationship of human diet to caries development; the identification and isolation of naturally occurring noncariogenic sweeteners and possible sucrose substitutes; the effects of sucrose substitutes with low cariogenic potential on growth, acid production and polysaccharide synthesis by oral bacteria; and the development of a slow release oral fluoride device, and fluoride mouthrinses and tablets. The role of fluoride in preventing dental caries has been established and NIDR continues to study the metabolic effects of various fluoride levels in humans, especially the effect of fluoride given prenatally and the mechanisms by which fluoride induces caries resistance in the child. Severe dental fluorosis is also under investigation.

In addition, studies are under way on the cellular and biochemical roles of vitamin A in the proper calcification of bone and dentin, the effects of various dietary lipids (saturated and unsaturated fats, cholesterol, and trans fatty acids) on salivary gland plasma membrane lipid composition, fluidity, enzyme activities, and saliva composition, and the effects of zinc deficiency on the stimulation of activity of epithelium lining in some regions of the oral cavity.

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases supports basic and clinical nutrition research that focuses on the function and requirements of specific nutrients, and the relationship of these nutrients and overall diet to health promotion, disease prevention, and disease treatment. In general, basic research on the metabolism of nutrients and their interactions deals primarily with specific nutrients rather than a particular disease, organ, or stage of life cycle.

Studies are under way on the metabolic role of specific dietary components, i.e., the essential amino acids and protein, carbohydrates, essential fatty acids and other lipids, vitamins, minerals, and dietary fiber. For example, tryptophan, tyrosine, and choline are being studied for their role in the formation of the neurotransmitters (serotonin, dopamine, and acetylcholine, respectively) as well as the subsequent effects on blood pressure, depression, and tardive dyskinesia. Noninvasive stable isotopes are being used to study the effect of dietary protein and energy intake on whole body amino acid metabolism with particular emphasis on alanine, glycine, and leucine. This research has opened up new approaches to estimating the amino acid requirements of healthy adults. Investigators are also studying the transport of peptides in the small intestine and kidney. Studies of fat metabolism examine the mechanisms of gastrointestinal fat digestion and absorption; the effects of dietary fat in the modification of microsomal chain elongation of fatty acids and thereby the fatty acid composition of tissue lipids; and the role of essential fatty acids in the diet on the regulation of bile acid synthesis and the formation of very low density lipoproteins.

Research on the fat soluble and water soluble vitamins attempts to clarify the mechanisms of metabolism and transport of vitamin A and its analogs, vitamin D and its metabolites, vitamin E, vitamin K, cobalamin, folate, thiamin, vitamin C, etc. For example, studies on the metabolism of vitamin A attempt to identify and isolate its metabolites and examine their roles in the maintenance of epithelial cells and keratinization of the skin. Studies on vitamin D examine its role in bone physiology in terms of its effect on calcium and phosphate absorption, as well as the hepatic regulation of vitamin levels during pregnancy. The mechanisms of folate absorption and utilization and folate binding proteins are investigated in order to develop a clearer understanding of folate deficiency states during pregnancy, in patients with intestinal diseases, in alcoholics, and in cancer patients. Studies of vitamin C attempt to establish appropriate levels of the vitamin for the treatment of osteoarthritis.

Studies on the trace minerals, i.e., iron, zinc, selenium, copper, silicon, chromium, tin, iodine, aluminum, molybdenum, magnesium, calcium, and phosphorous, provide important data on their metabolism, interrelationships, and overall relationship to human health. Imbalances or inadequacies of certain trace minerals are likely to promote metabolic adaptations that lead to chronic disease. Research continues on the biochemical basis of calcium absorption across the small intestine and the mechanisms of its regulation by vitamin D,

dietary calcium, growth and aging, etc.; the bioavailability of iron in foods and iron deficiency, particularly in terms of work performance and exercise capacity, as well as changes in the red blood cells; and the mechanisms of transferrin's function as an iron donor or acceptor in liver cells. Zinc status of certain segments of the population may reflect dietary inadequacies. Studies are under way to establish the use of saliva for the assessment of zinc status. Studies on dietary fiber examine its effect on stool transit time, digestion, rate of absorption, intestinal microflora, and interactions with nutrients, drugs, bile salts, and other substances.

Fundamental research on the mechanism of action of nutrients in absorption and metabolism, biological control of these processes, and the identification of other possible roles of nutrients and their metabolites provide important insight into the role of diet in the etiology of major diseases. Studies on the effect of diet on amino acid metabolism are particularly concerned with examining the mechanisms associated with the alterations of the metabolism of the branched chain amino acids found in liver failure, trauma, renal disease, urea cycle defects, diabetes, and starvation. Metabolism of sulfur amino acids is of particular concern in cases of homocystinuria, alcoholic liver disease, chronic liver disease, and neuropsychiatric disorders.

The clinical investigations supported by NIADDK relate to the assessment of nutritional status, the use of various nutritional support modalities, total parenteral nutrition, nutrient-drug interactions, and various diseases or conditions such as obesity, diabetes, osteoporosis, anemia, atherosclerosis, end-stage renal disease, and alcoholism. Studies on the effectiveness of total parenteral nutrition examine its effects on hormone levels and gastric secretions in patients; on protein and fat metabolism and the utilization of N_{15} as a tracer for protein metabolism and synthesis rates; and on calcium metabolism and bone disease in patients with gastrointestinal problems.

A major research priority of NIADDK is the investigation of the underlying causes of obesity with particular emphasis on prevention and control. Studies investigate the regulation of fat cell size and fat metabolism; total body composition; fuel mobilization and storage; the effects of meal pattern, diet-induced thermogenesis, and exercise on energy metabolism; thyroid function and thermogenesis; the factors affecting appetite, hunger, and diet selection; behavioral techniques for weight loss; and behavioral and genetic correlates of obesity. Studies on the biochemical and physiological mechanisms for the control of food intake examine the role of specific amino acids and other nutrients, as well as the role of insulin, the central nervous system, and the gastrointestinal hormone, pancreatic polypeptide, in the regulation of appetite and weight control in obese and in normal weight individuals. Other investigators examine the patterns of eating in the lean and the obese individual, the effects of under and overnutrition on changes in thyroid function and catecholamine metabolism and the resulting effects on thermogenesis, and the metabolism of brown adipose tissue in terms of its effect on the regulation of energy balance and dietary induced thermogenesis.

Determining the optimal diet, as well as the role of exercise and behavior modification techniques such as monetary incentives, for the treatment of obesity is an important component of this research, particularly in the treatment of obese children.

The U.S. Malnutrition Panel of the U.S.-Japan Cooperative Medical Sciences Program continues to be administered by NIADDK. The nutrition research fostered under the program investigates protein calorie malnutrition, and iron and vitamin A deficiencies. Solutions to these problems are primarily targeted to the undernourished populations of Asia and the Pacific Basin.

The NIADDK supports five Clinical Nutrition Research Units; namely, those located at the University of Chicago, University of Wisconsin, Vanderbilt University, the Medical College of Georgia, and Columbia University. The CNRU mechanism is stimulating progress in a multidisciplinary approach to clinical nutrition research, enhancing patient care, strengthening training environments in nutrition for medical students and other health professionals, and generating nutrition information for the public.

The National Institute of Neurological and Communicative Disorders and Stroke supports research on the dietary and metabolic factors that contribute to the growth, development, and overall health of the somatic (central and peripheral) and autonomic nervous systems. Nutrition studies in molecular biology, hemodynamics, and immunochemistry of the nervous system form the basis of many clinical investigations. Attempts to clarify the two-way interaction between nutrient intake and function of the central nervous system include studies on the effects of protein-calorie malnutrition and vitamin deficiencies on central nervous system metabolism and fetal development; the effect of plant and synthetic neurotoxins on the molecular and cellular mechanisms that underlie neuronal development, maintenance, degeneration and regeneration; the molecular mechanisms of neurotransmitter release, i.e., through changes in membrane lipids and calcium flux across the membrane as well as in conditions of vitamin deficiencies; and the mechanisms of nutrient transport and their metabolic products across the blood-brain and blood-cerebrospinal fluid barriers.

Studies are under way on the metabolic effects of nutrients on inborn errors of metabolism associated with neurological impairment and the influence of nutrients on the onset or progression of other neurological disorders. The role of lysine and its metabolites are being examined in relationship to sedation, sleep, and other neuronal functions associated with neurological disorders. Acute and chronic hyperaminoacidemias are being studied in terms of their effects on the regulation of amino acid and protein metabolism in the brain.

Basic studies examine the neural control of ingestive and drinking behaviors and the effect on appetite of the interaction between gustatory sense and olfaction. The role of zinc deficiency on disorders of taste and smell is under investigation, as well as the role of active and passive ion transport in taste and the effects of hormones

and various metabolic factors that may govern food preferences and intake. Investigators attempt to define the neural substrates through which gustatory afferent information elicits either ingestion or rejection of food in the oral cavity, as well as examine the peripheral modulatory influences on lateral preoptic, lateral hypothalamic, and thalamic taste nucleus neurons, and relevant neurotransmitters involved in ingestive behaviors. A particular neuropeptide cyclo-histidine-proline is being examined as a possible physiological modulator of normal appetite regulation since it has been shown to produce satiety.

The effect of diet on hormonal and metabolic regulations of ingestive behavior, energy homeostasis and expenditures, and weight loss is an important component of this research. The role of the central nervous system, particularly the monamine, norepinephrine, on energy homeostasis is being examined in terms of the occurrence of spontaneous obesity. Results from such studies are important for the prevention and treatment of obesity through various means including the development of anorectic agents used to control overeating.

Studies are carried out on the relationship between hypercholesterolemia and disturbances in auditory function, i.e., whether hypercholesterolemia affects auditory function and structure directly, or if, with hypercholesterolemia, the ear merely becomes more susceptible to damage from occupation or environmental noises. Other investigators examine the role of nutrition in cerebrovascular disease and stroke, and in post-traumatic epilepsy. Of particular interest is the use of intracerebral injections of aqueous solutions of ferrous or ferric salts in the prevention of post-traumatic epilepsy.

The National Institute of Allergy and Infectious Diseases promotes and supports research in the broad field of nutrition, infection, and immunity. Investigations focus on the mechanisms of food allergies in relation to the immune response to ingested antigens as well as the examination of various therapeutic strategies other than food elimination diets. Research is under way on the role and mechanisms of IgE mediated reactions to foods in the pathogenesis of atopic dermatitis.

Studies examine the modulating effect of specific nutrients such as amino acids, vitamins, minerals, and fatty acids on basic immune functions. Of particular interest are the modulating effects of iron on microbial virulence. The marine fish pathogen, Vibrio anguillarum, is a very efficient plasmid-mediated iron sequestering system. The bacteria proliferate in the host's body fluids and tissues where iron is complexed to iron binding proteins like transferrin and lactoferrin and thus is unavailable for bacteria use. Investigations are also carried out on the role of iron in the depression of toxin synthesis by Corynebacterium diphtheriae which inhibits cellular protein synthesis in susceptible animals and man; the characterization of the IgA antibody present in normal human serum which has a specificity for enterochelin, the iron transport compound produced by Escherichia coli and Salmonella typhimurium; the mechanisms of iron acquisition in Pseudomonas aeruginosa; and the molecular mechanisms of iron

assimilation in microorganisms and the transport of ferrous iron by strict anaerobes and facultative anaerobic bacteria. The role of Schistosoma hematobium infection and its treatment on the incidence of anemia and growth retardation of primary school children in Kenya is another area of investigation.

Additional studies are under way on the effect of malnutrition on resistance to infections, especially infectious diarrhea in children; the role of breast milk in defense against enteric infections; and the effect of infections on nutritional status. Investigators are examining leukocyte mobility in neonates and malnourished infants, the influence of endotoxins on zinc and copper metabolism, synergistic host defense role of fever and changes in plasma iron and copper levels, the effects of protein and zinc deficiency alone and in combination on the efficacy of BCG vaccine, and the role of arachidonate metabolism in host defense and inflammatory reactions. Other research is concerned with the effects of parenteral and enteral nutritional support of the patient on their immune function and hospital infections.

The National Institute of General Medical Sciences supports research directed to the discovery of better ways to prevent death from injury, mitigate pain, speed recovery of patients, and lessen the extent of disabilities caused by injuries. A better understanding is sought of the total body response to trauma, including burns. Studies are under way on the biochemical and physiological changes induced by trauma, and the fundamental aspects of wound healing and biological repair. For example, investigators are examining the sympathetic regulation of fat metabolism during sepsis; amino acid release from skeletal muscle and differences in control mechanisms following stress and trauma; hepatic glucose metabolism during shock; and physiological and biochemical alterations in specific organs such as the liver, which are initiated and integrated by neuroendocrine mechanisms used for the maintenance of homeostasis during shock.

Emphasis is also given to research on the treatment of post-traumatic infections, nutritional requirements of burn victims, and rehabilitation of injured patients. The NIGMS trauma and burn program supports research related to nutrition in the following areas: nutritional aspects of severe trauma and sepsis, new concepts in parenteral protein sparing therapy, branched chain amino acid feeding during injury, and cellular response in shock. The therapeutic value of fructose 1-6 diphosphate is being evaluated for treatment in several types of shock, i.e., hemorrhagic, endotoxin, tourniquet and burn shock. The effects of parenteral nutrition, especially the use of medium chain triglycerides, on the oxidation of fuel, protein synthesis and storage in the critically ill traumatized patient and septic patient, as well as on impaired cellular function and immunity in patients after surgery and trauma are also being studied. In addition, because diabetics appear to be more susceptible to sepsis, investigators are interested in the causative factors for major metabolic alterations in these patients that create a greater reliance on exogenously administered insulin. Data from this research will help to develop specific therapeutic modalities for the treatment of the diabetic patient with bacterial infections.

The National Institute of Child Health and Human Development research program focuses on the continuum of human development, from conception through infancy, childhood, and adolescence. The program emphasizes preventive approaches to nutrition-related conditions and stresses health promotion as well as disease prevention. Much of the research is multidisciplinary in nature and involves genetic, biochemical, developmental, anthropometric, behavioral, and cultural aspects of nutrition.

The NICHD has a strong interest in the area of maternal and infant nutrition and in elucidating the roles played by diet in infant development. Research interests focus on the nutrient requirements of normal, premature, and growth retarded infants, as well as on the composition of human milk, cows' milk, and synthetic formulas in relation to optimal infant nutrition. In some of this work, the interest centers on metabolic processes in neonatal adaptation, and on the role played by essential nutrients and other components of human milk in optimizing early development. Studies are under way on the amount and type of vitamin D metabolites required by the low birth weight infant and other neonates at various gestational ages, as well as on the interrelationships of the essential, exogenously derived, hematologic nutrients of tocopherol, selenium, iron, folate and vitamin B_{12} in the premature infant. For example, investigators examine the clinical and immunological status of premature newborns on diets with or without supplemental vitamin E, since this vitamin is important for the prevention of hemolytic anemia of prematurity, retrolental fibroplasia, and bronchopulmonary dysplasia. Other investigators examine the cellular factors that define or limit skeletal muscle growth potential and attempt to elucidate the mechanisms by which postnatal undernutrition may cause permanent growth retardation of skeletal muscle.

In order to assure optimum development in children, adequate nutrition should be provided to them in utero. Research continues to examine the complex relationship between the mother and her fetus in terms of nutrient transfer across the placenta, and to ascertain the effects of excessive or deficient amounts of certain nutrients on the morphologic and endocrine development of the fetus. Of particular interest is the placental transfer of oxygen, amino acids, vitamin A, iron, and folic acid. Studies have shown that dietary deficiencies of protein as well as of vitamin A in the mother cause fetal abnormalities in vitamin A metabolism, while deficiencies of iron in the mother also adversely affect the placental transfer of iron which is vital to fetal growth. Marginal deficiencies of folic acid during pregnancy are being examined in terms of its effect on growth and folic acid status of the newborn. Other investigations are under way to examine the effects of intrauterine malnutrition on neonatal lymphocyte function and the correlation between lymphocyte function and the risk of neonatal infections. Studies also are concerned with the relationship of serum folic acid levels of the mother on the etiology and prevention of neural tube defects, cranium bifidum and spinal bifida of the newborn, as well as the interaction of folate with zinc in fetal alcohol syndrome. Other studies of fetal alcohol

syndrome examine the effects of small doses of ethanol on morphology, morphometry, and functions of the hippocampal brain regions in zinc deficient animals. Calcium metabolism is also examined during pregnancy in terms of its hormonal control and its effects on intrauterine growth and postnatal development of the infant.

Most studies on nutritional aspects of developmental gastroenterology consist of basic research on cellular differentiation in relation to the functional development of the gastrointestinal tract. Human milk appears to provide specific components that stimulate functional development of the newborn's intestinal tract as well as digestive enzymes, such as lipases, which the infant is unable to produce in sufficient quantities. Studies examine carbohydrate tolerance of the infant by measuring the pulmonary excretion rate of hydrogen gas as an index of the functional capacity of the intestine to effectively utilize breast milk and commercial infant formula that contains the disaccharide lactose. Other investigators are studying the ability of infants between birth and 1 year of age to utilize starch through the development of salivary and pancreatic alpha-amylase and intestinal glucoamylase. The effects of various feeding methods and diets (cows' milk, soybean base, elemental formula, and total parenteral nutrition) on the development of pancreatic and salivary amylase are also examined. Studies are also progressing on digestive and absorptive disorders during infancy, particularly intractable diarrhea.

Studies on human milk and colostrum emphasize the conveyance of passive immunity to the young infant; the roles played by specific components of milk in stimulating cerebral and gastrointestinal development; the effect of maternal factors such as age, parity, nutritional status and duration of lactation on the composition of breast milk and colostrum; and neural and hormonal regulation of lactation. Research interests include the relationship of protein intake and trace metals to cerebral growth and function; the effect of nutritional deficits and excesses on physical growth and maturation; and the effect of non-nutritive food components, such as toxins, allergens, and contaminants, on the growth, development and health of children.

Studies are under way to examine the potential beneficial role of leukocytes present in human milk as well as other components that mediate the uptake of bound folate in the intestine of breast-fed infants. Investigators also attempt to isolate the intestinal receptor for the factor in breast milk that enhances folate absorption. Studies of the possible benefits and drawbacks of feeding the low birth weight infant with human milk versus infant formula consider the biochemical evidence of protein sufficiency or excess from both types of feeding in terms of the overall nutritional management of these infants. Another study evaluates the physical growth, immunological development, and gastrointestinal function of low birth weight infants fed human milk versus formula. Other studies examine the differences in the lipoprotein bile salt stimulated lipase activities and the macronutrient and electrolyte content of mature and preterm breast milk. The taurine, carnitine, and other amino acids in human milk are of particular interest, as well as the quantity,

distribution, and morphology of plasma membrane materials present in human milk. A major contract is developing human milk banking technologies for collection, storage, processing, and distribution of human milk and colostrum. The goal is to discover ways to preserve the labile nutritional and immunological components of human milk and colostrum during processing and storage.

Studies evaluate the antecedents and determinants of infant feeding practices; the frequency and duration of infant feeding practices of primiparae; the effects of westernization on feeding patterns among nomadic populations; the frequency and types of illnesses in infancy and early childhood as well as weight gain, physical growth, and behavioral characteristics as expressions of mother-child interactions in breast-fed versus formula-fed infants; and the relationship of maternal diet, alcohol and tobacco use during lactation to the physical and psychological growth and development of the infant. An epidemiological study is examining the relationship between types of infant feeding (human milk, cows' milk, or commercial formula) on serum cholesterol levels of children between the ages of 4-11 years. This study is testing the hypothesis that the high cholesterol content of breast milk establishes a homeostatic mechanism that allows for effective cholesterol metabolism in adult life. Other variables tested in the children include the effects of current age, sex, race, parental income, parental education, current weight, current diet, and age of introduction of solid foods on the relationship between type and duration of infant feeding and childhood serum cholesterol levels.

Research on dietary therapy of inborn errors of metabolism looks at abnormal metabolism of nutrient substrates. Included are investigations of the biochemistry and genetics of inborn errors which are, or may prove to be, treatable with diet. Many inborn errors of metabolism cause mental retardation or other disabilities of the central nervous system. Clinical research has shown that some of these diseases are amenable to nutritional management, as are a number of inherited metabolic diseases not associated with mental subnormality, such as lactase deficiency, cystic fibrosis, and some hereditary anemias. In most inborn errors of metabolism, the mechanisms by which aberrant levels of metabolic intermediates interfere with cerebral function remain unknown; neurochemical research in animal models, e.g., experimental phenylketonuria (PKU) and galactosemia, is being supported to answer this central question. One study of PKU is examining the point in time in which the initiation of diet therapy restricting phenylalanine can prevent the mental retardation, and physical and neurological growth changes in infants that occur with this inborn error of metabolism. Another study of maternal PKU investigates the biochemical and behavioral indices of fetal cerebral development in a normal and phenylketonuric environment, i.e., behavioral tests are selected to determine whether any of the biochemical abnormalities resulting from the simulated maternal PKU are associated with a delay in functional development, deficits in cognitive functions (spatial and memory), and changes in noncognitive behaviors (behavioral arousal and response inhibition).

Another study attempts to determine if iron therapy can correct the developmental deficits and behavioral abnormalities associated with iron deficiency anemia of infants. Investigators have shown a strong relationship between abnormal behavior, poor test performance, and impaired cognitive function in iron deficient, anemic infants. Further studies attempt to determine the level of iron depletion at which infant behavior is adversely affected; any differences between injectable and oral iron supplements on behavior; and whether iron therapy can correct the deficits and confirm specific patterns of behavioral disturbances. Results from this research will help to determine and develop preventive strategies, screening priorities, the level of iron deficiency requiring treatment, and the most efficient therapy for iron deficiency anemias.

Research on cultural and behavioral determinants of nutritional individuality includes studies of habits, taste and olfaction; food avoidances; and behavior modification of dietary intakes. Research on nutritional antecedents of adult disease focuses primarily on factors in the development of obesity in infancy, childhood, and adolescence. Behavioral, neurochemical, genetic, and hormonal factors involved in obesity are under investigation; the psychosocial and nutritional aspects of both adolescent obesity and anorexia nervosa are being studied. Studies examine the control of ingestion, appetite, and regulation of body weight in normal and obese infants. Obese children having one or two obese parents are being studied for energy balance, eating and exercise habits, self-evaluation skills and behavior patterns. Childhood obesity is also being studied in terms of its association with earlier eating and physical activity practices and parental attitudes. Examinations of resting metabolic rates, daily energy expenditure, and the thermogenic and hormonal responses to overfeeding are under way in obese adolescents. Changes in body composition and comparisons of energy expenditure help to clarify whether obese adolescents can dissipate excess calories derived from carbohydrate in the same way as the non-obese. Studies are under way to clarify whether fat or carbohydrate is the most appropriate source of energy for supporting the growth spurt in obese adolescents receiving hypocaloric dietary therapy and to determine if weight reduction in obese adolescents results in normalization of protein and glucose metabolism.

Since the patterns of adolescence usually persist into adulthood, and long-term consequences of eating behavior may involve diseases related to lifestyle such as heart disease, diabetes, hypertension, and cancer, studies are under way to examine the cognitive, developmental, social, and environmental factors that affect the processes that determine the patterns of food consumption during adolescence. Other investigations are under way on the complex relationship of malnutrition and social and health factors that affect the psychological development of children. These studies on the effects of malnutrition and environmental deprivation in child development hope to establish the extent to which it is possible to prevent retardation of physical and psychological growth by food supplementation and maternal tutoring. Studies also examine nutrition's role in diabetes in pregnancy and among infants of diabetic mothers. Studies on the

physiology and pathophysiology involved in the diabetic pregnancy permits a rational approach for decreasing fetal and neonatal deaths and morbidity in the offspring of the diabetic.

Other NICHD research emphasizes the development of new methods for assessing nutritional status, particularly during infancy, adolescence, pregnancy, and lactation. New noninvasive methods are being developed to measure serum ferritin, serum vitamin E, lactose absorption, and body composition. Mass spectrometric studies use stable isotopes of calcium, lecithin, and amino acids, while x-ray fluorescence spectroscopy and atomic absorption spectrophotometry are also being used.

Studies also investigate the effects of nutritional alterations on gonadotropin secretion, ovarian function and fertility. Research emphasizes the role of vitamins and minerals in sensitive reproductive processes (such as spermatogenesis), and the effects of oral contraceptives on the metabolism of folic acid, pyridoxine, and ascorbic acid. The reproductive consequences of low protein diets as reflected in gonadotropin production, fertility, and lactation are also under investigation.

The National Eye Institute supports research on the role of overall nutrition as well as specific nutrients, such as vitamins A and E, protein, copper, and zinc, on normal ocular and visual development, health and function. Studies also examine the association between nutritional imbalances and eye and vision disorders such as cataracts, retrolental fibroplasia, retinitis pigmentosa, gyrate atrophy, and childhood blindness.

The role of vitamin A in the visual process, particularly in the generation and recycling of rhodopsin, is an important research area since vitamin A deficiency is the leading cause of blindness in children living in the developing world countries. Investigators are studying the interaction in ocular tissue of vitamin A with other nutrients such as vitamin E and zinc; the role of binding proteins for retinoids in ocular tissue compartments; and the factors that modify their synthesis and metabolism. Studies examine the molecular structure of retinol binding proteins and their function in the eye since deficiencies of the proteins or altered binding specificity and affinity for retinol affect normal functioning of vitamin A in the retina and the pigment epithelium of dystrophic eyes. The proteins specific for retinol, 11-cis-retinal and retinoic acid, are being investigated in terms of their interactions with enzymes, proteins, and compartments known to be important in the metabolism of vitamin A in ocular tissues. In addition, investigators attempt to characterize and purify the enzyme retinol isomerase which is important for the isomerization of 11-cis-retinaldehyde in rhodopsin to all-trans retinaldehyde, as well as to define possible links between isomerization and available energy systems, and to determine the mode of intercellular transfer of vitamin A from pigment epithelium to the rods.

Other studies examine whether postprandial changes in plasma amino acids, ethanol consumption, or diabetes influence the uptake of tyrosine and tryptophan at the retinal-blood barrier; tyrosine and tryptophan are the precursors for dopamine and melatonin respectively; both are important in the regulation of light sensitivity in the eyes. Differences in dietary protein and fat are also investigated in terms of how they alter ocular membrane structure and function. Of particular interest are alterations in membrane phospholipids that influence intercellular transport of calcium, copper, and zinc and its consequential effects on the visual process and the development of retinopathies.

Research findings have shown that pharmacological doses of specific nutrients, particularly vitamin E, may protect ocular tissue against various retinopathies. For example, vitamin E's role in reducing the incidence and severity of retrolental fibroplasia in the premature infant and in protecting the eye from the cytotoxic effects of accumulated natural or induced oxidants is being investigated. In addition, topical application or parenteral administration of ascorbate and citrate are being investigated in terms of reducing corneal ulcerations and perforations in the alkali burned eye. The use of an arginine deficient diet in the treatment of gyrate atrophy is also an area of research. The corneal uptake and metabolism of topically applied retinoids are being studied in terms of efficacy of their use in the treatment of xerophthalmia and the promotion of corneal wound healing.

Studies are under way on the effect of specific nutrient deficiencies, such as vitamins A, E, ascorbic acid, riboflavin, tryptophan, and taurine, zinc, selenium, and copper, on the eye. Imbalances in these nutrients are being considered as possible risk factors for cataract development. Vitamin E deficiency is under investigation since it causes changes in the outer segments of photoreceptors and a buildup of autofluorescent pigment within the pigment epithelium; with time these may cause a total loss of photoreceptors and the appearance of autofluorescent pigment in all retinal layers. Zinc deficiency is known to have an adverse effect on vision due to an increased accumulation of electron dense inclusion bodies in the retinal pigment epithelium (RPE) cells, which, along with the photoreceptor outer segments, subsequently undergo severe degeneration. Dietary excesses of selenium have been shown to be related to an increased incidence of cataracts. Other studies on the development of cataracts investigate the relationship between changes in cations and water balance in the lens, the regulation of calcium levels in the lens, calcium's role in maintaining membrane permeability of the lens, and lens changes in experimental hypocalcemic cataracts. Investigations also examine the visual system's ability to recover from trauma in terms of the effect of specific nutrients on the ocular immune responses.

The National Institute of Environmental Health Sciences supports research on the biological risks and toxic adverse effects of environmental agents such as food-borne contaminants and additives on biological systems.

Food toxicology research examines naturally occurring products, such as those present as food plant components or mycotoxins (aflatoxins), as well as chemical agents intentionally introduced to foods as additives or unintentionally as environmental contaminants. Food toxicants and toxic alterations of the absorption, metabolic and excretory functions of the gastrointestinal tract are being investigated not only in terms of their role as biological stressors, but also to understand how the toxicant interacts with other environmental contaminants.

Studies attempt to determine the mutagenicity of food-borne toxicants to Salmonella typhimurium and to human lymphoblasts, and their carcinogenicity in rodents; the formation and detection of n-nitroso compounds and hydroxamates, products of pyrolysis of amino acids, proteins, and other food materials; and reaction products of peroxidizing lipids and cholesterol oxidation. The influence of diet on carcinogenicity of amino acid pyrolysis products and DNA damage caused by carcinogens in rat tissue is under investigation; and studies of aflatoxin B_1 carcinogenesis using the trout model are examining whether carcinogenesis can be inhibited by diet using biologically relevant doses and exposure patterns. Other studies of carcinogens are concerned with the polycyclic aromatic hydrocarbon carcinogens (PAHC) that appear to cause increased proliferation and accelerated size increases in spontaneous fibrous lesions that appear to be precursors of atherosclerotic plaques. Cholesterol feeding is being tested as to whether it exacerbates the development of lesions and whether active protease inhibitors, retinyl acetate or aspirin, added to the diet interfere with lesion development. This research provides valuable information as to the promotional nature of the carcinogens, the early steps and processes associated with growth and development of spontaneous lesions, and the role of dietary supplements to modify the process of atherosclerotic plaque formation.

In addition, the effects of heavy metal intake on the metabolism and balance of essential elements are being examined. For example, studies are under way to investigate the consequences of long-term selenium intake and the possible adverse health effects of some selenium compounds; and the influence of diet and maturation of the intestine on the mechanisms of heavy metal absorption and distribution from the perfused lumen of the jejunum; and the accumulation of these metals in the jejunal mucosa (i.e., lead, cadmium, mercury, copper and nickel are being examined for metal interactions and for specificity of transport inhibitors). Chronic administration of lead is being investigated for its effect on absorptive functions of the gastrointestinal tract because it appears to be related to altered fecal output, increased urinary delta-aminolevulinic acid, anemia, and anorexia. In addition, cadmium and mercury are being studied in terms of their role in amino acid transport and renal function and in the development of nephrotoxicity. Additional studies seek to determine toxic changes generated in the enterohepatic, biliary, and renal systems by environmental contaminants and the alteration of these systems to prevent biological insults through decreased absorption and enhanced secretion. These studies hope to clarify how natural food products such as mycotoxins or their metabolites are

generated in the body; the specific mechanisms of food toxicity; the interactions of food-borne contaminants with other environmental agents that increase or decrease toxicity; and the health risks associated with exposure to food contaminants.

Other studies investigate contaminants resulting from food storage generated under suboptimal storage conditions. Food processing hazards such as nitrites, nitrates, and other additives are being studied to learn how they are altered in the foodstuff and how they are transformed by biological systems. Studies also attempt to determine chronic effects of small concentrations of ozone on the metabolism of rats and mice in the presence of normal and high levels of polyunsaturated fatty acids in the diet, and in the presence and absence of vitamin E and DPPD, a synthetic antioxidant. The effects of ozone on vitamin E metabolism and of linoleic acid oxidation in vivo is of particular interest.

The National Institute on Aging supports basic and clinical investigations on nutrition's role in the aging process. For example, studies are under way on the effects of food restriction on increased life span, and the effect of nutritional status on immune function and on the structure and function of several tissues, including adipose, hepatic, brain, muscular, skeletal, and vascular tissues. A variety of nutrient manipulations are being investigated in terms of their effects on longevity, as well as on the age of onset and nature of age-related diseases and changes in adipose tissue physiology, metabolism and hormonal components of blood serum, hepatic lipid metabolism, skeletal muscle function, functional properties of arteries, and bone loss. Protein undernutrition, in particular, is being examined in terms of possible neurochemical changes in the hypothalamus-pituitary-gonadal axis of rats with age. Other studies examine the effects of diet, especially that supplemented with the catecholamine precursor l-tryptophan, on ovarian function with age. Research continues to examine the normal nutrient requirements of the elderly, as well as requirements altered by disease or chronic drug regimens.

Studies on the effects that various age-related physiological changes may have on nutritional status focus on changes in renal physiology, intestinal physiology, taste and smell, salivary secretions, and dentition. Such physiological changes affect food intake and the digestion and absorption of necessary nutrients. It is thought that aging dulls the common chemical taste sense that registers the spicy and sharp components of substances like vinegar, salt, horseradish, carbonated beverages, as well as the sense of smell. Researchers are attempting to separate out true sensory losses from cognitive changes with age in order to develop ways to improve the pleasure of eating for the elderly and thereby possibly improve their nutritional status.

Also under investigation is the relationship between nutritional status and subsequent morbidity and mortality among the elderly in terms of such diseases as cancer, coronary heart disease, stroke, and osteoporosis. For example, studies address the role of vitamin D in calcium transport and subsequent bone turnover in postmenopausal

women, as well as the effect of protein malnutrition on reduced immune function often found in the elderly. Variations in bone resorption and its effects on the rapid and dynamic relationship between the contribution of bone and diet to blood calcium levels are being quantified during various treatments with vitamin D, calcium, fluoride, etc. In addition, deficiencies of vitamin D, zinc, and folate have been found in several of the aged populations in the U.S. In light of these findings, investigators are studying why some elderly individuals have a decreased plasma level of 25-hydroxy vitamin D concentration and if this vitamin abnormality developed along with or independently of changes in calcium homeostasis. Researchers are also investigating the influence of age on the ability of the skin to photosynthesize adequate amounts of vitamin D_3. Another study in animals of various ages is investigating the ways in which aging influences zinc metabolism and the response of the aged animals to suboptimal levels of dietary zinc. Folate deficiency is being studied in terms of decreased intestinal folate absorption with aging as well as the possible influence of drugs impeding folate absorption.

The Division of Research Resources provides support for important resources needed for the performance of research in nutrition. Many investigators funded by the categorical institutes of NIH for nutrition research use DRR's resources. DRR administers and manages five programs that serve health researchers at universities, hospitals, and research institutes throughout the United States. These programs are the General Clinical Research Centers, Biomedical Research Technology Program, Animal Resources, Biomedical Research Support, and Minority Biomedical Research Support. During FY 1983 all of these programs supported nutrition research.

The General Clinical Research Centers Program (GCRC) is composed of 74 specialized centers in major hospitals throughout the United States where more than 3,000 protocols are pursued annually by clinical researchers. The program supports 80 percent of all the inpatient care costs awarded by the NIH. In addition, an extensive outpatient activity is conducted within the existing centers. The range of studies related to nutrition, on both inpatients and outpatients, includes all aspects of research in nutrition, health, and disease. These centers conduct clinical nutrition studies on atherosclerosis, cancer, diabetes, environmental health factors, hyperlipidemias, obesity, parenteral nutrition, and vitamins. Two hundred and forty full-time dietary personnel are working on the GCRC's, and dietary interns spend training periods there. Most of the centers have a diet kitchen. The GCRC Program is providing support for young clinical investigators who want to pursue a career in clinical research. Several of these clinical associate physicians are involved in clinical nutrition research.

The objective of DRR's Biomedical Research Support Program is to strengthen and enhance the research environment of institutions engaged in health-related research, through the use of flexible funds and local decisionmaking which enable them to more efficiently and effectively conduct their biomedical research programs. Appropriate

uses of awarded funds include pilot research studies, support of new investigators, unexpected research requirements and emergencies, and central shared research resources.

The overall objective of the Animal Resources Program is to support resource projects that provide, or enable scientists to most effectively use, laboratory animals in human health-related research. The objective is accomplished through the Regional Primate Research Centers Program and the Laboratory Animal Sciences Program. Particular attention is given to animal resource activities that are supportive of the categorical interests of NIH. An important research area supported under this program is nutrition.

The Biomedical Research Technology Program uses specialized facilities and expertise in the physical sciences to create biomedically relevant technologies and to make these technologies accessible to biomedical scientists across the country. A number of these facilities are used to support research in nutrition.

The Minority Biomedical Research Support Program provides funds to institutions having significant enrollments of minorities. The funds are used to provide opportunities for minorities to participate in the conduct of biomedical research, some of which are in the area of nutrition.

In summary, the Institutes with mandates in categorical diseases support nutrition research programs in their areas of responsibility in both the prevention and the treatment of disease; namely, NCI on diet and cancer; NHLBI on diet and heart, lung and blood disorders; NIDR on nutrition and dental caries; NIGMS on nutrition and trauma including burns; and NEI on nutrition and various eye disorders. NIADDK, NICHD, and NIA support nutrition research particularly related to nutrient requirements relevant to the different stages of the life cycle and specific metabolic and genetic diseases. NINCDS supports research on nutrient intake and metabolic changes as these affect the nervous system in health (growth and development) and disease; NIAID on the role of nutrition on infection and immune system function; and NIEHS on the effect of environmental agents such as food contaminants and additives on biological systems. Through studies in biochemistry, physiology, and cell biology, NIH supported research aims to elucidate fundamental mechanisms in order to synthesize the results into practical information on nutrition and diet that will assist the individual to develop normally, and to live as long and as healthy a life as possible.

Manpower Development

Manpower development in nutrition research is enhanced through Research Career Development Awards (RCDA's) and New Investigator Research Awards (NIRA's). In FY 1983, 130 awards were given for a total of $3,488,000.

RCDA's: In FY 1983, 57 awards in nutrition were given by NCI, NEI, NHLBI, NIA, NIADDK, NIAID, NICHD, NIDR and NIGMS for a total obligation of $1,183,000. The type and number of awards given are as follows:

- o "Research Scientist Development Awards" support scientists, who are committed to research and need advanced research training and additional experience (1 award).

- o "Modified Research Career Development Awards" foster the development of young scientists with outstanding research potential for careers of independent research in the sciences related to health (31 awards).

- o "Research Career Awards" enable institutions to finance positions favorable to the intellectual growth and research productivity of established investigators of high competence for the duration of their careers (4 awards).

- o "Academic/Teacher Awards" create and encourage a stimulating approach to disease specific curricula that will attract high-quality students, foster academic career development of promising young teacher-investigators, develop and implement excellent multidisciplinary curricula through an interchange of ideas, and enable the grantee institution to strengthen its existing teaching program. The academic and teacher investigator awards are not used by all of the B/I/D's (16 awards).

- o "Clinical Investigator Awards" provide the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members to pursue research aspects of categorical areas applicable to the awarding unit, and aid in filling the important academic faculty gap in these shortage areas within health professional institutions of the country (5 awards).

Recipients of these awards conduct nutrition research in the areas of metabolism, human growth and development, nutrition and cancer, and cardiovascular and lung diseases. Examples of the studies in each of these areas are:

- o Metabolic studies include research on: metabolic and endocrine aspects of obesity; regulation of human gastric responses to meals; hypothalamic control of body weight and feeding; evaluations of dietary alterations and treatments; epidemiology of digestive diseases; neural and humoral control of mucosal transport; study of nutritional and hemolytic anemias; gastrointestinal digestion and absorption of fats; development and control of hepatic and renal gluconeogenesis; intestinal absorption of calories and minerals in man; metabolic role of cobalamin and folate; folate supply and utilization; protein nutrition in experimental uremia; calcium binding proteins and the vitamin D endocrine system; glycerol-3-phosphate dehydrogenase and egg yolk avidin; metabolic effects of burn injury and sepsis; the physiological role of esterified vitamin A in photoreceptor cells and the interaction between photoreceptors and pigment epithelial cells; resonance raman microscopy of visual photoreceptors; and the biochemistry of oral tissues, secretions, and diseases.

- Studies on human growth and development include research on: nutrition and development of adipose tissue, i.e., lipoprotein lipase activity related to feeding behavior; the role of glucose production in the developmental maturation of neonatal carbohydrate homeostasis; developmental aspects of renal transport and experimental models of Fanconi syndrome; breath analysis for carbohydrate absorption in neonates; chemical studies in growth and development; nutrient transport in the developing intestine and colon; the appropriate forms and levels of vitamin D supplements for preterm and term infants; dietary habits during childhood and etiology of breast cancer or other diseases in later years; pathogenic mechanisms for impaired leukocyte mobility in pediatric patients having severe protein-calorie malnutrition; and pediatric aspects of diabetes mellitus.

- Investigations on nutrition and cancer include research on: the biosynthesis of mammalian glycoproteins; lipids and membrane structures of leukemic leukocytes; asparagine biosynthesis in normal and tumor cells; hexosaminidase levels and diet; human mucosal structure and function; and normal and tumor cell regulation of folate polyglutamate synthesis.

- In the areas of cardiovascular and lung disease, research includes: the regulation of cholesterol metabolism in cultured cells; coronary risk, family lifestyle and behavior change; outcomes of behavioral programs for chronic obstructive pulmonary disease and diabetes; the effects of diet on blood pressure; the effects of nutrition, age, and drugs on lung hyperoxia; preventive cardiology; and oxidants, stress and pulmonary prostaglandin metabolism.

NIRA's are used also by the NIH as a mechanism for manpower development in nutrition. The NIRA (R23) encourages new investigators (including those who have interrupted early promising research careers) in basic or clinical science disciplines to develop their research activities within the program interests of NIH. This special grant-supported program provides funds to help bridge the transition from training status to that of established investigator. In FY 1983, 73 new investigator research awards were given for a total obligation of $2,305,000 by NCI, NEI, NHLBI, NIA, NIADDK, NIAID, NICHD, NIGMS, and NINCDS.

The areas under study by the 73 recipients of these awards include metabolism in growth and development, fat metabolism and obesity, vitamin and trace mineral metabolism, immune function, eye disorders, trauma, hypertension and cardiovascular disease, and cancer. Studies in each of these areas are given below.

- Studies on metabolism in growth and development include research on pregnancy and lactation, infant feeding, gastrointestinal development, neuroendocrine control, and total parenteral nutrition.

Research includes: effects of malnutrition on pregnancy or lactation; characterization and bioavailability of manganese binding molecules in human milk, cows' milk and infant formula; influence of differences in the protein/calorie ratio and energy intake on the rate and composition of growth of small premature infants; dietary and metabolic manipulations of lactose absorption in the intestine; the effects of qualitative and quantitative changes of dietary protein on the activity of the mucosal component of protein digestion in an animal model of pancreatic insufficiency; characterization of compositional and organizational changes in the microvillus membrane (MVM) of the gastrointestinal tract from suckling, weaning, and postweaned rats in terms of the qualitative (breast milk vs. artificial formula), quantitative (volume of milk ingested, duration of weaning period), and changes in nutrients provided during the perinatal period; the effects of postnatal diet, endocrine milieu, and increased bile acid pool on mediating the development of hepatic bile acid transport in the human infant; postnatal development of bile secretory, metabolic and structural functions of the liver; effect of nutrition on neonatal intestinal metabolism, specifically those factors controlling substrate oxidation in rat intestine during suckling, weaning, and postweaning periods; and effects of diet on attention span, activity level, anxiety, hyperactivity, aggression, and tantrums in 4-year-old children.

Studies include research on the evaluation of neuroendocrine control (i.e., the role of histamine) of drinking elicited by eating; the influence of feeding cycles on circadian body temperature rhythm in rats; neurological basis of taste-elicited ingestion and rejection of foods; and effects of foodstuffs such as carbohydrates and amino acids, on the functioning of neurons within the enteric nervous system of the cat; behavioral/observational assessments of food intake, physical activity, and parental influences on children's food intake and physical activity, as well as the relationship of these parameters to energy balance. Studies are also carried out on interactions of hormones, dietary fat, carbohydrates, and amino acids on leucine metabolism in the liver; and metabolism of dietary sulfur amino acids in altered liver function.

Research continues on the metabolic alterations induced by total parenteral nutrition in the rat; and intestinal membrane structure and functional development.

o Research in the area of fat metabolism and obesity includes studies on the effect of energy intake on the rate and composition of weight gain in premature infants; effects of dietary intervention with food restriction on weight loss in obese (FA/FA) rats; and regulation of fat and protein synthesis.

Other studies include research on kinetics of lipolysis, i.e., the effect of diet on the roles of lipoprotein lipase and hepatic lipase in the interconversion of triglyceride-rich lipopro-

teins in normal and hyperlipidemic plasma; the effect of weight loss and exercise on lipoprotein lipase; kinetic and biochemical modifications of lipoprotein lipase; regulation of cholesterol esterification in the intestine; and biliary tract motility in the fasting and fed state.

Other research includes studies on the role of beta endorphins on feeding and obesity; opioid peptides' effects on food intake, selection, and obesity; regulation of experimental obesity via the sympathetic adrenal axis; neurobehavioral analysis of glucagon on satiety; aerobic training and efficiency of energy utilization in animals; and contribution of energy yielding nutrients to hepatic fat accumulation.

- Studies on vitamin and trace mineral metabolism include determination of the subcellular localization of vitamin A in mammalian epithelium tissues of the intestine, cornea, testis, and liver; characterization of B_6 dependency in I-mice, an inbred strain of mice that may serve as an animal model for a B_6 responsive genetic disease; the effects of changes in vitamin D metabolism during pregnancy on fetal growth and skeletal development; mechanisms and pathways of intestinal absorption of vitamin D sterols in rats, emphasizing factors influencing absorption that may be altered in gastrointestinal disease; and tocopherol status of patients with potentially compromised vitamin E status due to malnutrition and stress due to hyperoxia.

  Other studies include research on the biological utilization of molybdenum; zinc nutrition and intestinal absorption of cholesterol, i.e., the intestinal absorption of dietary cholesterol, the chemical and physical characteristics of chylomicrons formed during active intestinal transport of cholesterol, and the metabolic turnover of chylomicron cholesterol as affected by the nutritional status of zinc; trace mineral bioavailability and metabolism studies; factors that influence the choline and methionine content in milk and tissue choline concentrations; and cellular mechanisms of chloride absorption and secretion by rabbit colon.

- Studies on immune function include research on intestinal and hepatic defense mechanisms in immature animals using known hepatotoxins (proteases and endotoxins) prior to and following gavage feeding in breast-fed and bottle-fed animals; the effect of Schistosoma hematobium infection on nutritional status, i.e., anemia, growth, and physical fitness of school-age children in Kenya and the benefits of a safe and inexpensive oral drug on nutritional status; investigation of reduced host defense and nutritional status in the elderly determined by complete nutritional, hematological, and immunological assessments; effects of total parenteral nutrition systems and parenteral phospholipid infusions on cholesterol homeostasis in man; investigations on the effect of circulating IgG antibody on the uptake of enteric antigen in neonatal rabbits; and changes in the morphology and metabolism of megakaryocytes and platelets

in guinea pigs with cholesterol feeding and acute and chronic ethanol ingestion.

- Studies on eye disorders include research on cytosol retinoid binding proteins (from the retina, pigment epithelium, testes, and liver of several species of animals) in order to understand their molecular structure, functions in the eye, and effect of deficiencies on altered retinol binding specificity and affinity; immunobiology of ocular surface Langerhans cells, i.e., changes in distribution, density, and membrane antigens/receptors of the cells in response to vitamin A deficiency; biochemical differences in the proteins, glycoproteins, and proteoglycans, and in the antiproteases in the eyes of vitamin A deficient animals that might account for the rapid corneal ulceration and stromal degradation that occurs in keratomalacia; corneal uptake and metabolism of topically applied retinoids with respect to their efficacy in the treatment of xerophthalmia and promotion of corneal wound healing; and the role of phosphorylation of the vitamin A pigment rhodopsin in vision and the role of calcium levels in regulating the phosphorylation process.

  Other studies include research on the role of excitatory amino acids in the visual process vis-a-vis the photoreceptors and bipolar cell transmitters in the retina of fish, amphibians, and mammals; epidermal lipids and disorders of keratinization; and mechanisms that determine normal copper concentrations within intraocular compartments as well as those that cause an elevation in copper concentrations in intraocular fluids after an episode of uveitis.

- Studies on hypertension and cardiovascular disease include measurement of cardiovascular parameters during maximal exercise (i.e., oxygen consumption, cardiac output, stroke volume, heart rate, and O_2 extraction), as well as the measurement of pulmonary function, serum lipids, body composition, glucose tolerance, and echocardiographic left ventricular function in young (<25 years) and older (>50 years) athletes matched on the basis of training and performance; and alterations in the plasma lipoprotein profile, hepatic lipoprotein production, skeletal muscle and adipose tissue lipoprotein lipase activity, and vessel and tissue pathology as influenced by age, exercise, diet and hyperlipemia in individuals.

  Other studies include the effect of exercise training on 60-year-old sedentary individuals in terms of O_2 uptake, glucose tolerance, plasma insulin levels, and the development of coronary artery disease; effects of exercise and restricted feeding on the age-related physiological and biochemical changes in the mammalian heart with old age; and effectiveness, safety, and mechanism of the cholesterol-lowering effect of high glucose diets in normal subjects and patients with familial hypercholesterolemia (FH).

- Studies on cancer include growth and differentiation of mast cells and T cells; sodium ions and mitogenic signaling; deoxyribonucleoside triphosphate metabolism; metabolism of N-13 ammonia and L-amino acids in murine tumors which are sensitive or resistant to glutaminase or asparaginase therapy; modulation of the development of normal granulocyte/monocyte colony forming cells by 12-O-tetradecanoylphorbol-13-acetate (TPA), retinoic acid, and prostaglandin E1; antitumorigenic effects of the pineal gland in nutritionally restricted rats; lymphocyte carcinogen metabolism in acute leukemia; receptors for reduced folates in human tissues important for the regulation of folate uptake and transport in normal cells as well as mutant cells; screening for dietary inhibitors of N-nitrosamine carcinogenesis; and relaxation training to reduce aversion to chemotherapy.

- Studies on trauma include hypermetabolism after severe head injury in children; and intravenous lipid metabolism following burns.

Program Development

A major responsibility of the NCC is to identify areas for further research and bring them to the attention of the scientific community through the development and publication of program announcements (PA's), requests for applications (RFA's), and requests for proposals (RFP's).

A PA is a formal statement of an NIH extramural research activity or of the initiation of a new or modified mechanism of support. It may describe new or modified program interests, or simply be a reminder of continuing interest.

An RFA is a formal statement which (a) invites grant applications in a well-defined scientific area to accomplish specific program purposes, (b) generally identifies only one application receipt date, and (c) indicates whether or not funds have been set aside for the competition and, if so, the amount of funds and/or the expected number of awards to be made. An RFA may be reissued as necessary.

An RFP is the government's invitation to prospective offerors to submit a contract proposal based on the terms and conditions set forth in the RFP by the statement of work that describes the nature of intended procurement. The number of contracts awarded as a result of an RFP is smaller than the number of applications funded as a result of PA's and RFA's.

Table VII lists the 19 PA's, RFA's, and RFP's in nutrition published in FY 1983, with the origin and date of each announcement, the type of announcement, and its title. A brief description of each announcement follows the table. Included in the table are six PA's, six RFA's, and seven RFP's.

TABLE VII

PA's, RFA's, and RFP's in Nutrition Research and Training
Published In The NIH Guide For Grants and Contracts, FY 1983

ISSUED BY	DATE	TYPE	TITLE
NHLBI	12/1/82	RFP	"Longitudinal Studies of Coronary Heart Disease Risk Factors in Young Adults"
NCI	1/17/83	RFP	"Epidemiologic Study of Black/White Differences in Cancer Patient Survival"
NHLBI	1/28/83	PA	"School Health Promotion and Cardiovascular Health of Children and Adolescents"
NICHD	2/28/83	RFP	"A Prospective Study of the Frequency and Duration of Infant-Feeding Practices Among Primiparae"
NIDR	3/4/83	RFP	"Effect of Severe Dental Fluorosis on the Oral Health of Adults"
NIDR	3/18/83	RFP	"Development of Device to Measure Intraoral Plaque pH"
NICHD	4/11/83	RFP	"Successive Small-For-Gestational Age Births: A Longitudinal Study of Fetal Growth and Perinatal Outcome"
NCI	5/20/83	PA	"National Research Service Awards"
NIA	5/20/83	PA	"Cellular Aging Research: Differentiated Cells in Culture"
NCI	5/20/83	RFA	"The Role of Micro and Macronutrients in the Prevention of Cancer"
NICHD	6/13/83	RFP	"Effects of Maternal Phenylketonuria (PKU) on Pregnancy Outcome"
NIA	6/17/83	PA	"Health and Effective Functioning in the Middle and Later Years"
NCI	7/15/83	RFA	"A Phase III Trial of a Low Fat Diet in Women with Stage II Breast Cancer"
NICHD	7/15/83	PA	"Behavioral/Biomedical Interdisciplinary Research Training"
NCI	8/19/83	RFA	"New Natural and Synthetic Inhibitors of Carcinogenesis"

(Table VII Continued)

ISSUED BY	DATE	TYPE	TITLE
NIADDK	9/23/83	RFA	"Cooperative Clinical Study of Dietary Modification on the Course of Progressive Renal Disease"
NCI	9/23/83	RFA	"Cancer Control Science Program: Program Projects"
NCI	9/23/83	RFA	"Cancer Control Research Units"
NHLBI	9/23/83	PA	"Hypertensive Rat Resource--Dahl Model"

The RFP, "Longitudinal Studies of Coronary Heart Disease (CHD) Risk Factors in Young Adults," issued by NHLBI, sought proposals for a 5-year longitudinal study of the precursors to and the concomitants of changes in CHD risk factors in a biracial population of young adult men and women. Three to six centers are anticipated to study the relationships among risk factors, life styles, and their changes in cohorts of black and white males and females initially 18 to 32 years of age. Some risk factors for CHD, i.e., obesity, hypertension, and hypercholesterolemia, may be partially determined by genetic factors or habits that are formed in infancy, childhood and adolescence and some risk factors do not change dramatically before the late teen years. Investigations are needed to examine the interrelationships among those risk factors known to increase in young adulthood with a significant change in lifestyle. For example, data suggest that weight gain is pronounced during the late teen years through 30 years, particularly in males, and that a linear relationship exists between weight and lipoprotein fractions. Studies need to determine the interaction of life events, behavior, and changes in physical activity and dietary intake that may influence weight gain and lipoprotein levels as well as the importance of weight gain in relation to risk factor changes during this age span. Changes in CHD risk factors include blood lipids and lipoproteins, blood pressure, alcohol consumption, "pill" use, and behavior patterns.

The RFP, "Epidemiologic Study of Black/White Differences in Cancer Patient Survival," issued by NCI, sought proposals for a prospective study to identify factors that explain black/white survival differences for patients with invasive or in situ cancers of the female breast, colon (excluding rectum), urinary bladder or corpus. Among the possible explanatory variables are delay differences that impact on the extent of disease at diagnosis, differences in host vulnerability (e.g. nutritional status, and overall health status), differences in tumor histology and in treatment patterns independent of stage at diagnosis. The data collected will include, but not be limited to, nutrition information, alcohol consumption, smoking history, socioeconomic indicators, prior estrogen use, and family history of cancer, treatment including compliance, morphological characteristics of the primary tumor.

The PA, "School Health Promotion and Cardiovascular Health of Children and Adolescents," issued by NHLBI, encouraged applications in the area of demonstration and education research in cardiovascular school health promotion. Cardiovascular disease, the leading cause of death in the U.S., is not solely a problem of adults. The atherosclerotic process may begin in childhood in susceptible individuals and progress during adolescence and young adulthood even though serious clinical manifestations usually do not appear until middle age or later. The comprehensive school health program is one approach for investigating the determinants of good cardiovascular health habits and their maintenance in early preschool through high school age groups. Research should address those factors that may contribute to the role of school health promotion in the adoption of good cardiovascular health behaviors in children and adolescents, i.e., the precursors and determinants of the development and maintenance of behaviors conducive to cardiovascular health such as sound nutrition, nonsmoking, and physical activity.

The RFP, "A Prospective Study of the Frequency and Duration of Infant Feeding Practices Among Primiparae," issued by NICHD, sought proposals for a prospective study to acquire data and information from primiparae that would help to determine the frequency of breast-and bottle-feeding at several intervals up to 1 year, and to describe the influence of certain factors on choice and duration of breast and bottle-feeding. The following conditions or factors that may interfere with or promote breast or bottle feeding will be evaluated: pre- and post-natal medical services; mother's perception of the supportiveness of her peers, family and medical environment; maternal beliefs about infant-feeding; confidence and enthusiasm towards breast-feeding; physiological conditions of the mother and infant that may interfere with breast-feeding; the initial feeding pattern as well as the change(s) in the pattern over time; and sociodemographic characteristics. Of particular interest is an analysis of the relationship between factors underlying the claim of insufficient milk, maternal employment, and duration of breast-feeding. Knowledge of the factors that affect choice and early cessation of breast-feeding is necessary for the formulation of effective strategies to assist in the establishment and maintenance of lactation.

The RFP, "Effect of Severe Dental Fluorosis on the Oral Health of Adults," issued by NIDR, sought proposals for a cross-sectional epidemiologic survey to assess among lifetime adult residents of an area with severe endemic dental fluorosis several variables of oral health (e.g., dental caries, tooth loss, attrition) most likely to show the adverse effects of having severe dental fluorosis. Two comparable study populations of adults who have since birth ingested community drinking water shall be compared; one group shall have consumed water with fluorides at an optimal concentration recommended for the geographic area while the other group consumed a water supply with at least four times the optimal fluoride concentration. Multiple study sites will be accepted due to the requirement of a relatively large number of adults (200 in each study group) with lifelong exposure to fluorides. The communities shall have a documented 60-year history of

natural fluoride concentrations in the community water. The study should help to provide much needed and timely data on whether excessive fluoride levels in water supplies pose any hazards to the oral health of adults.

The RFP, "Development of Device to Measure Intraoral Plaque pH," issued by NIDR, sought proposals to develop a device that can measure plaque pH under normal circumstances using either nonwire telemetry or storing the data in a miniature portal device. This pH sensor should allow the measurement of acid produced in the plaque as a result of food ingestion. Acid is produced within dental plaque from the bacterial fermentation of carbohydrates by Streptococcus mutans. This acidic plaque is the cause of the demineralization of tooth enamel. The proposed work shall be done in the following two phases: the development of a pH sensor capable of being incorporated into an intra-oral appliance, and the development of an intraoral appliance compatible with the sensor and equipped with the most promising sealed pH sensor(s).

The RFP, "Successive Small-For-Gestational Age Births: A Longitudinal Study of Fetal Growth and Perinatal Outcome," issued by NICHD, sought proposals for a longitudinal prospective study of fetal growth and perinatal outcome of women at risk of delivering small-for-gestational-age births (defined as birth weight less than the 10th percentile for gestational age). The study is to identify at risk mothers for intrauterine growth retardation using ultrasound during the second and early third trimesters of pregnancy, to collect interview and prenatal medical data, to distinguish the two primary types of fetal growth retardation at birth, to evaluate postnatal growth during the first year of life in order to detect either catch-up accelerated growth or continued slow growth, and to assess the known risk factors (maternal smoking, underweight of malnourished mothers and hypertension or other medical factors) and any newly identified risk factors using a geographically-based population of pregnant women. Specific nutrition factors to be ascertained from 1,500 expectant mothers in their second and third trimesters of pregnancy include: dietary habits before becoming pregnant; a 24-hour log of dietary intake taken at three times during the second and third trimesters; fat deposition at three time intervals during the second and third trimesters; and metabolic tests including an oral glucose tolerance test obtained in the second trimester.

The PA, "National Research Service Awards Act," issued by NCI, solicited applications for research training grants, individual postdoctoral fellowships, and senior postdoctoral fellowships in all the basic and applied sciences relevant to cancer. Predoctoral and postdoctoral research training in nutrition as it relates to cancer is one of the twelve areas highlighted in the PA under the major heading of Preventive Oncology. Surgical and radiation oncology are the other two major research areas of interest.

The PA, "Cellular Aging Research: Differentiated Cells in Culture," issued by NIA, sought applications for further research and training activities on the mechanisms of cellular aging through utilization of

tissue and organ specific cells in culture. The use of differentiated cells in culture provides an excellent opportunity to study age-associated alterations in differentiated functions that are expressed by cells in vitro and, therefore, to increase our understanding of the mechanisms of age-related functional decline in various tissues and organs. The areas of growth and nutrition, somatic cell genetics, and various aspects of cellular, molecular, and developmental biology as they pertain to differentiated cells are of interest. Studies are encouraged to investigate the nutritional requirements for the establishment of normal differentiated cell strains capable of expressing differentiated traits and perturbations or procedures that alter, inhibit or delay age-related changes in differentiated functions.

The RFA, "The Role of Micro and Macronutrients in the Prevention of Cancer," issued by NCI, solicited applications for cooperative agreements to support risk reduction clinical trials to study the effect of micro or macronutrients on cancer risks in humans. Micronutrients include, but are not limited to the following: beta-carotene, vitamin A or analogs, vitamin C, selenium and alpha-tocopherol. The macronutrients include fats, vegetables, fruits, cereals and fibers. Epidemiological studies and laboratory research results support the concept that the incidence of cancer may be influenced by the levels of nutrients and nonnutritive substances in the diet. For example, the level of dietary fat has shown a positive correlation with the incidence of cancer of several sites while fiber intake has shown a negative correlation with the incidence of cancer at several sites. Since dietary manipulations of the administration of certain compounds have been reported to be effective in interfering with carcinogenesis in animals and since epidemiological studies suggest a possible negative association of certain dietary factors with cancer incidence, clinical intervention trials are now encouraged. Of particular interest are trials involving normal populations, populations known to be at risk but free of neoplasia, and high risk populations with identified precursor or precancerous lesions.

The RFP, "Effects of Maternal Phenylketonuria (PKU) on Pregnancy Outcome," issued by NICHD, sought proposals for a study to determine the best method of managing women during pregnancy who have hyperphenylalaninemia (classical PKU, hyperphenylalaninemic variants or atypical PKU) in order to reduce the number of offspring born with mental retardation, microcephaly, major congenital anomalies, particularly congenital heart defects, intrauterine growth retardation, and fetal wastage. The study is to determine the level of maternal phenylalanine that will maintain a normal pregnancy; at what stage of pregnancy a low phenylalanine diet is most effective in preventing the effects of maternal PKU on the developing fetus; if the beneficial effects of a low phenylalanine diet can be improved when initiated prior to conception compared to post conception; whether the diet reduces the frequency of mental retardation, spontaneous abortions, low birth weight, congenital malformations, neurological and behavioral impairment found in infants of mothers with hyperphenylalaninemia; and the levels of tyrosine and trace metals during pregnancy, and if low, whether supplementation affects pregnancy outcome.

The PA, "Health and Effective Functioning in the Middle and Later Years," issued by NIA, sought applications for basic research studies to specify the mechanisms and conditions that influence health and effective functioning during the middle and later years, i.e., that can extend the productive middle years of life by preventing, postponing or reversing current disabilities of old age. Due to the linkages among behavioral, social, and biomedical processes, proposals will often require the formation of multidisciplinary teams. One of the issues of interest is nutrition, exercise and sleep which includes research in the following areas: psychosocial factors influencing age-related changes in food preferences, eating habits and nutrition; cohort differences in nutrition and the consequences for health in the middle and later years of life; long-term and short-term effects on health and effective functioning of various types of exercise; and psychosocial factors in etiology and therapies for age-related sleep disorders and behavioral consequences of age-related sleep disorders.

The RFA, "A Phase III Trial of a Low Fat Diet in Women with Stage II Breast Cancer" issued by NCI, sought applications for cooperative agreements to support participation in a multi-institution randomized clinical trial of a low fat diet (20 percent of calories) aimed at prolonging the disease-free survival and overall survival in surgically staged breast cancer patients who have involvement of the axillary lymph nodes. Applications are considered either from clinical units, nutritional coordinating units, or statistical coordinating units. The following items are relevant to applications from nutrition coordinating units: an initial course of instruction for nutritionists from the participating clinical units, including written instructional materials for patients and a workshop; the development of food shopping plans, menus, recipes, etc. to be used by patients; plans to convert dietary data into nutrient content data with a maximum 2-week turn around time and to send this data to the clinical and statistical units via use of computer software and databases; and plans for quality control on all phases of dietary modification. The investigators will identify, enroll and follow participants in this clinical trial using a protocol developed jointly by the investigators and the NCI staff. Since investigators are supported through the cooperative agreement mechanism, an assistance relationship will exist between NCI and the awardees to accomplish this activity. The NCI is involved in the development of the protocol for the trial, monitoring adherence to the protocol, monitoring the safety of the study participants, and coordination of the project.

The PA, "Behavioral/Biomedical Interdisciplinary Research Training," issued by NICHD, encouraged applications for National Research Service Awards (NRSA) for both individual postdoctoral fellowships and institutional training grants for pre and postdoctoral trainees in order to support individuals for research in the interdisciplinary area of behavior and biomedicine. In order to understand the complex interactions between basic biological mechanisms underlying development and the behavioral determinants of development, applications for interdisciplinary research training are encouraged in the areas of behavior and nutrition, developmental genetics, behavioral pediatrics, developmental behavioral pharmacology, and developmental behavioral biology.

In the area of behavior and nutrition, studies are encouraged on the failure to thrive in infants, obesity, learning deficits, hyperactivity, anorexia, control of appetite and satiety, and nutritional factors in brain/behavioral development.

The RFA, "New Natural and Synthetic Inhibitors of Carcinogenesis," issued by NCI, invites applications for studies to determine the extent to which inhibitors of carcinogenesis occur naturally, as in foods consumed by man. Studies are needed on the potential role of these substances as cancer preventive agents, i.e., their mechanisms of action and their pharmacokinetic properties. The four areas of research emphasis are as follows: (1) The identification of new naturally occurring inhibitors with special attention paid to appropriate methods of isolation of specific constituents or chemical forms. Isolation, purification, and identification procedures that are developed for these inhibitors should represent quantitative, reproducible, and analytical methods that will permit analyses of their precise content. (2) The identification of mechanisms of action of the inhibitors in order to determine the biochemical and biological basis for the inhibition, i.e., to study the absorption, distribution, metabolism and excretion of natural inhibitors of carcinogenesis. (3) The improvement of current systems and development of new systems needed to identify and study naturally occurring inhibitors. This need exists for both in vivo and in vitro systems and for both short-term reliable assay systems and systems for long-term studies. (4) The determination of the range of conditions under which efficacy of natural inhibitors is demonstrable. Investigations should include dose-response studies, species in which inhibition can be demonstrated, the range of carcinogens or spontaneous tumor against which activity exists, the antipromoting activity of the natural inhibitor or its activity during the post initiation period, etc.

The RFA, "Cooperative Clinical Study of Dietary Modification on the Course of Progressive Renal Failure," issued by NIADDK, sought applications from investigators willing to participate with NIADDK in a cooperative agreement program for a multicenter cooperative clinical study to define the influence of controlled nutritional intervention on the progression of chronic renal disease/renal insufficiency. Evidence from animal studies indicates that maladaptation of the mechanisms that normally emerge to compensate for glomerular injury can be attenuated by dietary restriction of protein and/or concomitant phosphates. Moreover, the impact of dietary restriction on overall health, nutritional status and life quality of protein restricted individuals needs to be addressed. The clinical study will consist of the following four sequential phases: development of protocol and operations manual, limited pilot studies, full-scale cooperative study, and data analysis and reporting. Approximately 10 clinical centers are anticipated to participate in each phase. The protocol is likely to include adults with chronic progressive renal diseases with glomerular filtration rates < 50 percent of normal at study entry. Patients with chronic glomerulonephritis should comprise the major study group who would receive a low protein/low phosphate test diet most likely derived from ordinary food processing with supplementation of essential nutrients to fulfill nutritional requirements.

The RFA, "Cancer Control Science Program: Program Projects," issued by NCI, sought applications for the establishment of Cancer Control Science programs (CCSP) that will plan and implement focused research studies aimed at major cancer control problems. Cancer control is defined as the reduction of cancer incidence, morbidity, and mortality through an orderly sequence from research on interventions and their impact in defined populations to the broad, systematic application of the research results. Cancer control is also viewed as either prevention (primary and secondary) or management (diagnosis, pretreatment evaluation, treatment, rehabilitation and continuing care). The proposed research program should have a clearly identified theme or "program" and consist of an integrated group of projects from cancer control research phases II through V (i.e., II. Methods development and testing, III. Controlled intervention trials to establish cause and effect relationships, IV. Research in defined populations, and V. Demonstration and implementation studies). The group of projects is expected to result in a greater contribution to stated program goals than if each project were pursued separately and is expected to require long-term support with multidisciplinary participation and collaboration. The four areas emphasized in prevention research are diet and nutrition, chemoprevention, occupational cancer control, and screening and early detection of cancer.

The RFA, "Cancer Control Research Units," issued by NCI, sought applications for the establishment of Cancer Control Research Units (CCRU) that will plan and implement focused research studies aimed at major cancer control problems. This research will include innovative intervention studies aimed at reducing cancer incidence, morbidity and mortality and which are generalizable to larger populations. The proposed CCRU should have one or more clearly identified "themes" or programs each consisting of an integrated group of projects from cancer control phases II and IV. One of the four specific program areas of research interest to the CCRU's is the Prevention Program where the emphasis is on research studies to identify, evaluate, and implement techniques and approaches for the prevention and early detection of cancer. Diet and nutrition, chemoprevention, occupational cancer control, and screening and early detection of cancer are the four general areas of prevention research emphasized in the Prevention Program. The other program areas of research interest to the CCRU's are: the Community Oncology Program; Cancer Control Science Program; and the Smoking, Tobacco and Cancer Program. The CCRU will be a long-term resource for research and training for the Cancer Control Program of the NCI.

The PA, "Hypertensive Rat Resource--The Dahl Model," issued by NHLBI, sought applications for a self-supporting resource for hypertensive rats, i.e., the Dahl model consisting of the following two strains, the S strain that develops hypertension on a high salt diet and the R strain that remains normotensive on a high salt diet. The S strain develops hypertension from early adulthood, however, a lifelong low salt diet can prevent its development. The R strain, however, remains normotensive at any age at any level of dietary salt. The hypertensive research community has accepted and used the Dahl model for over

a decade and greater numbers of the model are expected given the following considerations: many of the hypertension mechanisms are influenced by a high salt diet; the interplay of genetics and environment, i.e., diet, stress, drug response, etc., in hypertension can best be studied in a rigorously controlled model; and salt induced hypertension is a high priority research area. Breeders will be selected to establish and operate a pilot colony consisting of five breeding pairs of S rats and five breeding pairs of R rats for a period of 6 months. A single breeder will be selected on the basis of overall performance.

Nutrition Conferences Sponsored by the NIH

Each year the NIH sponsors a number of conferences on a variety of nutrition topics that reflect the current interest of the Institutes in areas of program development for nutrition research and training. Such conferences also help to expedite transfer of nutrition technology to scientists and educators so as to assure the appropriate application of research in practice. Table VIII lists the 12 conferences held in FY 1983.

TABLE VIII

NIH SPONSORED NUTRITION CONFERENCES, FY 1983

INSTITUTE	DATE	TITLE
NIADDK, NICHD NHLBI, FIC	Oct.17-19, 1982	Workshop on the Classification of Obesities
NIADDK, U.S.-Japan Malnutrition Panels	Dec. 7-8, 1982	Practical Approaches to Eradication of Subclinical Iron Deficiency
NHLBI	Jan. 1983	Workshop--Changing Patterns of Cardiovascular Disease in Pacific Basin
NIADDK, NICHD NIGMS, NINCDS NEI, DRR	Mar.19, 1983	U.S.-Japan Workshop on Research in Inborn Errors of Metabolism
NHLBI	Apr.25-26, 1983	Workshop on Dietary Management in the Prevention or Reversal of Blood Lipid Elevations Induced by Antihypertensive Medication
NINCDS	Jun.2-3, 1983	Human Taste and Smell: Measurements and Uses
NIADDK	Jun.29, 1983	Workshop on Nutrition Research Opportunities in Long-Term TPN
NIADDK, NHLBI NICHD	Jul.3-8, 1983	FASEB Summer Research Conference on Trace Elements
NICHD	Jul.17-20, 1983	Intrauterine Growth Retardation
NCI,NIADDK, NICHD, FIC	Aug. 7-11, 1983	Western Hemisphere Nutrition Congress VII
NHLBI	Sep.15-16, 1983	Working Conference on Research Methodologies in School Health Promotion
NHLBI	Sep.27-29, 1983	Consensus Conference on Treatment of Hypertriglyceridemia

THE INTRAMURAL RESEARCH PROGRAM

The total cost of the NIH intramural program in biomedical and behavioral nutrition research was $8,818,000 for FY 1983 (see table I). Institutes supporting intramural research in nutrition include NCI, NHLBI, NIDR, NIADDK, NIAID, NICHD, NEI, and NIA. Most of this research takes place on the NIH campus in Bethesda; however, the NIA intramural program is located at the Gerontology Research Center in Baltimore, Maryland.

A major component of the intramural nutrition research program are the interagency reimbursement agreements of two Institutes (NIA and NCI) with the National Center for Health Statistics (NCHS) for the epidemiological followup of participants of the Health and Nutrition Examination Survey (NHANES I). This survey, conducted in 1971-74, collected dietary, biochemical, clinical, and anthropometric information on the nutritional status of a national sample of the U.S. population comprising 23,000 persons between the ages of 6 months and 74 years. The dietary data collected included calorie intake; calories as a proportion of RDA calories; nutrient density; protein, carbohydrate, and fat as a proportion of total calories; number of carbohydrate servings per day; proportion of carbohydrate servings from complex carbohydrate sources, and proportion of carbohydrate sources from individual food groups. The major emphasis of the followup survey is to relate the previously assessed dietary intake and biochemical test findings, chronic disease risk factors, environmental and occupational exposure, and the psychosocial characteristics of the population with morbidity and mortality occurring since the original survey.

The NIA study includes a cohort of 14,400 persons, who were between the ages of 25 and 74 years at the time of the original study, in order to obtain specific information on dietary practices, alcohol use, exercise, smoking and changes in behavior over the past 10 years. Weight and blood pressure measurements are being made and related to previous measurements in order to assess changes in risk factors over time. The relationship between various nutritional factors and subsequent health status of the elderly is of particular interest in the hopes of improving the quality of life for all elderly persons.

NCI is utilizing the NHANES I data to examine regional differences in vitamin A and vitamin C intake, and fruit and vegetable intake in relation to the observed North-South gradient in colon, rectal, and breast cancer mortality. The intake of vitamin A, retinol, carotene, and vitamin C (based on 24-hour recalls); the intake of vitamins A and C (based on food frequencies); the frequency of fruit and vegetable consumption; and serum vitamin A levels are being compared. Using 24-hour dietary recall data, individual foods are being ranked by their contribution to total vitamin A intake for various age-sex-race region subpopulations. This information is being used in developing dietary interviews that will assess vitamin A intake and its relationship to cancer risk. In addition, the possible relationships between vitamin intake, biochemical and other indices of nutri-

tional status, and subsequent health status including trends in potential risk factors for cancer will be examined over time.

Also, NCI is examining the possible effects of various factors (including diet, age, sex, race, poverty status, pregnancy-lactation status, region of inhabitancy, and individual variation) on serum vitamin A levels in a national sample of 14,000 adults from NHANES I. The serum vitamin A levels are of interest since some prospective studies have shown that mean serum vitamin A levels are lower among those persons who develop cancer. A specific hypothesis being tested is whether serum vitamin A levels are significantly affected by vitamin A intake within a well-fed population such as the U.S.

Another component of NCI's research evaluates the NHANES I dietary and anthropometric data from 100 women between the ages of 12 and 18 years as predictors of age at menarche and in relation to the development of breast cancer.

Other NCI studies under way examine the relationship between nutrition and cancer etiology through basic research at the molecular level, particularly of cancer chemoprevention with vitamin A and its analogs. Dietary habits and nutrient consumption of selected cohort populations are being analyzed in relation to the incidence of different cancers, with investigations under way on general nutritional status, anthropometric and biochemical indices, as well as cooking practices. Another research priority is the assessment of the efficacy of total parenteral nutrition (TPN) for the support of the cancer patient.

Studies of vitamin A and its synthetic analogs, the retinoids, have shown that supplementation with retinoids can reverse tissue metaplasia and neoplasia in various laboratory models through the restoration of normal cell differentiation, and when given to animals can prevent chemical and viral induced carcinogenesis. Phase I studies are now under way to examine three new oral synthetic retinoids in terms of their basic pharmacokinetics, recommended doses, maximum doses, and drug toxicity. The maximum duration of continuous treatment will be 6 months. These drugs are also being tested for their possible therapeutic use for the dermatological conditions of acne, psoriasis, disorders of keratinization (ichthyoses and Dariers' disease), basal cell carcinoma, and other related dermatological disorders, as well as to establish safe and tolerated doses for Phase II-III chemoprevention trials.

Skin cancer chemoprevention through the use of vitamin A involves extensive research on the morphological effects, biochemical mechanisms, metabolic pathways, and dose-toxicity of synthetic vitamin A (13-cis-retinoic acid) and its analogs in cell cultures and laboratory animals. Also, a 5-year randomized double-blind clinical trial of 1,800 subjects at 10 participating centers is currently examining the effectiveness of low doses (10 mg/day) of isotretinoin in reducing the incidence of basal cell carcinomas in a high risk population and the possible side effects associated with the long-term administration of such low doses. Case reports have shown that isotretinoin

can prevent the appearance of new basal cell carcinomas for 4 years in patients at high risk of developing new tumors. Such research has provided important information on the cellular and molecular basis of skin carcinogenesis as well as the therapeutic value and antipromoting properties of vitamin A, both before and after the onset of malignancy.

Basic studies on the effects of retinoids on tumor cell growth have shown that in the presence of retinol or retinoic acid, spontaneously transformed mouse fibroblasts (BALB/c-3T 12-3 cells) stop growing at a lower saturation density (approximately 120,000 cells/cm^2). Retinoid treatment also enhanced the adhesion of cells to the culture vessel surface and to each other. Other studies on the biochemical actions of vitamin A analyze the subcellular fractions of rat liver for the topical distribution of mannosyl transferase that glycosylates the lipid intermediate retinyl phosphate and the polyisoprenoid derivative dolichyl phosphate. In vitamin A deficiency, the liver pools of retinyl palmitate and retinyl phosphate are depleted, however, dolichyl phosphate levels increased fourfold. This same depletion of retinyl palmitate and retinyl phosphate occur in transplanted as well as primary rat hepatoma tissue. The vitamin A depletion of the tumor tissue is thought to be either the consequence of cell selection during carcinogenesis or a permissive condition for the development of tumor from initiated cells.

Other studies are investigating the alteration of carcinogenesis in the liver by the dietary lipotropes choline, methionine, folic acid, and vitamin B_{12}. The hypothesis that physiological methyl deficiency promotes hepatocarcinogenesis is being tested by determining the carcinogenic and liver tumor promotion activities of methyl deficient diets, and the effects of dietary methyl donors on the tumorigenic activities of epigenetic carcinogens and tumor promoters. The study attempts to establish the relationship between methyl insufficiency and the promotion of liver cancer as a result of the hypomethylation of DNA.

Studies of the murine L1210 leukemia cells which are resistant to L-phenylalanine mustard (L-PAM) have shown that these cells can be sensitized to L-PAM in vitro and in vivo by reducing the cellular concentration of glutathione either through pharmacological or nutritional means. The in vivo reduction of glutathione in the tumor cell through nutrition is accomplished by the use of defined amino acid diets devoid of L-cystine and with a reduction of L-methionine.

Experimental systems have also been established for assessing the effects of fatty acids on the growth of normal cells as well as on carcinogen-induced mammary tumors in rats. Studies have shown that all of the unsaturated fatty acids present in the mammary glands in appreciable amounts promote cell growth. Oleic acid appears to promote the maximum growth rate of tumor cells, while linoleic or linolenic acid promote maximum growth of normal cells. Both normal and tumor cells are inhibited by saturated fatty acids.

Some studies have shown that exogenous insulin administered to sarcoma-bearing rats increases spontaneous food intake, nitrogen balance, and gain in body weight, but decreases muscle catabolism (3-methylhistidine) without stimulating tumor growth. The animals treated with insulin do not have a longer survival, but do have a greater carcass mass and accrual of both protein and fat similar to that of normal body composition. Exogenous insulin appears to preserve the host without feeding the tumor.

The physiological basis for cancer cachexia is also under investigation with physiological and behavioral control of food and water intake being measured in normal and cancerous animals. An in vitro assay for protein synthesis and breakdown has been developed by incubating weanling rats' extremity muscles in a physiological buffer system. Test sera from normal, cachetic, and septic animals are added to the system in order to determine whether a circulating factor is present in the sera that decreases protein synthesis and increases protein catabolism. In addition, an in vivo assay used to determine the cachetic factor involves the administration of sera from cancer-bearing animals that are not eating to normal animals and then measuring food intake. If such a factor does appear from these assays, investigators will attempt to determine whether it is a tumor-derived factor or a host-derived factor responding to the tumor and then to biochemically characterize the factor.

Cancer cachexia and malnutrition of the host can impair physical defense barriers and may also impede granulocyte recovery. Studies are under way to determine the influence of variations in protein/carbohydrate intake on cyclophosphamide (CP) induced myelosuppression. The aim of these studies is to develop methods that define patients at high risk for infection and to improve the ability to diagnose infections early, treat them effectively, and ultimately prevent them.

Animal studies as well as epidemiological studies have been used to assess the role of specific dietary factors in cancer prevention. Information on such agents appears to be lacking in terms of their quality and form in the food supply, bioavailability, biochemical effects, and interactions with other nutrients. In cooperation with the Beltsville Human Nutrition Research Center, the Division of Cancer Prevention and Control (DCPC) is developing the analytical methods for the routine analysis of nutrients and investigating the pharmacodynamics and interactions of dietary factors identified as possible cancer preventive agents.

Selenium is one dietary factor considered as possibly important for the prevention of cancer and therefore is being analyzed for its pharmokinetics and bioavailability. The initial phase of the selenium studies examines the pharmacokinetics of a single dose of sodium selenite (inorganic form) and selenomethionine (organic form) in a healthy population having an adequate baseline selenium intake. The parameters measured include percent absorption, maximum concentration, and half-life for single doses in both fasting and nonfasting individuals. In addition, the bioavailability and health effects of

multiple doses of inorganic and organic selenium will be examined and compared in terms of their absorption, distribution, and excretion. Other studies will correlate the dietary intake of beta-carotene with beta-carotene, retinol and retinol binding proteins in the blood as well as the interaction of dietary fat and fiber intake on mineral and vitamin metabolism.

Two additional efforts of DCPC under way to ensure the standardization of data on selected variables associated with the incidence of cancer are the development of a core questionnaire that will collect a common data base on smoking, diet, and occupation and psychosocial variables; and a dietary assessment questionnaire used as part of the core questionnaire for use in a large clinical trial as well as determining individual dietary intakes. Another study assesses whether it is possible to gather accurate information about an individual's past dietary intake. These instruments which allow for the collection of baseline data in an identical manner will help to improve the interpretation of results from different studies, facilitate the resolution of conflicting data, and enhance the comparability of results from the different clinical trials that address the issues of nutrition and cancer.

Several case control and cross cultural surveys are under way to study the incidence of cancers of the colon, breast, esophagus, lung, pancreas, and stomach in relation to dietary patterns of specific populations, biochemical and anthropometric indices, and general nutritional status. Case control studies have been initiated in high risk areas with unusually high mortality rates from cancer. For example, three studies are being carried out in Finland: One 5-year study examines the possible chemopreventive effects of a daily beta-carotene supplement of 15 mg given to cigarette smokers on the incidence of lung cancer. The second, a case control study on breast cancer, investigates the relationship of serum levels and dietary intake of selenium, vitamins A, E, and C, fats, and other nutrients on the incidence of breast cancer in individuals with benign breast disease. The third study examines the associations between various dietary components and different cancers using dietary history information that was previously collected from a subgroup of the population that developed cancer.

In order to assess the efficacy of TPN as a means of nutritional support for the cancer bearing host, prospective randomized studies of TPN as an adjunct to aggressive chemotherapy and radiation treatment are under way. Cancer patients receiving TPN are examined for deficiencies in vitamins, trace metals (zinc, copper, and chromium), and essential fatty acids, as well as for changes in gluconeogenesis, protein synthesis, glucose disposal, body composition for potassium, alanine kinetics, mineral balance, and requirements for all known nutrients.

Also within the intramural program, the Office of Cancer Communications has begun its Cancer Prevention Awareness Program which is providing messages to the public that proclaim that changes in dietary habits (e.g., increasing fiber, reducing fat intake) can reduce an individual's risk of cancer.

NHLBI has several intramural investigations that attempt to clarify the structure, biosynthesis, transport and metabolism of lipoproteins since their moieties (i.e., cholesterol esters, triglycerides, and apoproteins) are significant in the development of atherosclerosis and coronary heart disease. The apolipoprotein composition of plasma lipoproteins is considered as the governing factor in directing lipoprotein metabolism. Knowledge of the stoichiometry and equilibrium constants for the specific apolipoprotein complexes (A-I, A-II, C-I, C-III, E, and H) formed in the plasma has provided a framework for evaluating the rate that apolipoproteins control lipid metabolism, e.g. cholesterol and triglyceride transport. It has been shown that apolipoprotein E (apo E) is important in modulating the catabolism of triglyceride-rich lipoproteins, and that apo E-II, an abnormal form of apo E, is associated with type III hyperlipoproteinemia and is associated with decreased concentrations of low density lipoproteins (LDL). Individuals with apo E-II experience elevations in triglycerides after a high fat meal along with an increased production of apo E.

Other conditions resulting from abnormal apolipoprotein metabolism are Tangier disease and familial hypercholesterolemia. Individuals with Tangier disease have an abnormal apo A-I that is catabolized more rapidly than in normal individuals. This causes low HDL concentrations in the blood. Patients with familial hypercholesterolemia (FH) have decreased plasma concentrations of apo A-I and increased concentrations of apo E. The LDL receptor activity in these patients is highly correlated with plasma cholesterol levels, severity of clinical disease, and response to treatment. Determination of apolipoprotein levels in patients with premature coronary artery disease showed that levels of apolipoprotein A-I and C-II, rather than plasma cholesterol and triglyceride levels, were more clearly identified within this atherosclerotic population. In order to further examine the apolipoproteins found in various dyslipoproteinemic individuals, a new two-dimensional electrophoretic technique is being used to determine apolipoprotein concentrations, molecular weight, and apolipoprotein variants.

Other studies are under way to examine the pathophysiology of the dyslipidemias and to increase our understanding of normal lipoprotein physiology. These include investigation of the effects of the different lipoproteins and apolipoproteins on lipid metabolism of various cell types (i.e., fibroblasts, macrophages, and hepatocytes) in normal as well as dyslipidemic individuals. Cellular metabolism has been investigated in persons with FH, abetalipoproteinemia, Wolman's disease, cholesteryl ester storage disease, Tangier disease, and Erdheim-Chester disease. The adult human liver appears to have specific receptor or recognition sites for apo A-I, E, and B. Analysis of these hepatic receptors in several dyslipidemic states has shown specific genetic and physiological control of the receptors.

In addition to lipoprotein and apoprotein, per se, investigators are also quantitatively evaluating the molecular properties of lipopro-

tein lipase and hepatic lipase, two enzymes responsible for triglyceride hydrolysis. The activity of both enzymes will be studied in normals as well as in individuals with disorders of lipid metabolism, and correlated with lipid and apolipoprotein concentrations in the blood.

Research also continues on the control of blood pressure by restriction of dietary sodium intake and the activity of the sympathetic nervous system. Individuals with essential hypertension can be categorized as salt-sensitive or non-salt-sensitive depending on whether blood pressure increases or remains the same when sodium intake is increased from 9 to 249 mEq/day. Normally, when sodium intake is increased, sympathetic activity is decreased and the dopaminergic nervous system, a mediator of the body's natriuretic response, is stimulated. The sympathetic nervous system is thought to be an etiologic factor in essential hypertension, while the role of the dopaminergic system is unclear. In one study, salt-sensitive patients did not show the suppression of sympathetic activity with decreases in plasma and urinary norepinephrine levels that normally occur when a low sodium intake is changed to a high sodium intake. Thus, the persistence of increased sympathetic activity in these individuals might reflect impaired sodium excretion that caused the increase in blood pressure. In non-salt-sensitive individuals with essential hypertension, the plasma and urinary norepinephrine decreased during high salt intake and urinary dopamine increased. Thus, the increased dopaminergic activity may be a factor in the development of hypertension in the non-salt-sensitive individuals.

Another study of male Sprague-Dawley rats is measuring the impact of excess dietary salt on sodium homeostasis of the thymocyte cell. Both intracellular sodium content and 22-Na efflux are being measured. Research will continue to investigate the possible mechanisms, such as sodium pump inhibitors, related to the regulation of blood pressure.

Studies under way as part of NIDR's intramural program examine the effects of sugar substitutes on growth, acid production, and glucose synthesis by Streptococcus mutans in the mouth. Data have shown that the sucrose derivatives palatinose and palatinit did not support growth or acid formation by several different species of oral streptococci, that these compounds inhibited glucan formation by S. mutans, and that xylitol also inhibited growth and acid production by S. mutans, S. sanguis, S. mitior and A. viscosus. Another non-sucrose sweetener--acesulfam K--which is 300-350 times sweeter than sucrose was also investigated in terms of caries development in rats and found to be noncariogenic.

Because plaque pH is known to affect caries development, a device is being tested that would measure the pH of intraoral plaque when challenged with different foods. A fluoride releasing device is also being investigated in rats for its anticaries effects. Data indicate that the marked reduction of caries produced by the device was due to the topical effects of fluoride. The effectiveness of fluoride mouthrinses and tablets given to school children beginning

in kindergarten and first grade and continued for 8 and 9 years is being studied in terms of reducing the incidence of caries. Other studies investigate the anomalies in taste perceptions with procedures that quantify not only taste detection thresholds but also the intensity and pleasantness of various taste stimuli when provided at commonly encountered intensity levels.

NIADDK conducts nutritional studies that attempt to determine the metabolic roles of various nutrients in the body and the effects of different levels of nutrient intake on metabolism and physiological function. For example, studies are being done to determine if rats on different diets produce multiple types of very low density lipoproteins (VLDL) which differ in their apo B components. Other studies examine the transport of fatty acids between capillary lumen and the interior of parenchymal cells. Data support the concept that lipolytic products travel in the outer leaflets of cell membranes and that they can form lamellar extensions of the leaflets under certain conditions. In addition, studies that have purified lingual (pharyngeal) lipase have shown that bile salts--particularly sodium taurodeoxycholate--and calcium ions together greatly enhance the action of lingual lipase on the metabolism of long chain triacyglycerol. Findings from this research indicate that lingual lipase can act on dietary fat in the small intestine and thereby could be helpful in cases of pancreatic insufficiency.

Many studies are investigating the action of insulin in the regulation of glucose transport and metabolism. Some preliminary evidence suggests that insulin's stimulatory action on glucose transport in isolated rat adipose cells occurs through a subcellular redistribution of glucose transporters rapidly cycling in an exocytic/endocytic-like fashion; insulin acts at a step whereby glucose transporters associated with the plasma membrane become functional, and cAMP-mediated counter-regulation of insulin-stimulated glucose transport by catecholamines comprises both the regulation of the subcellular distribution of glucose transporters and the modulation of the activity of those glucose transporters present in the plasma membrane. Insulin also appears to stimulate glucose transport in isolated guinea pigs and human adipose cells and rat diaphragm through this same translocation mechanism. Basic research investigations under way have also shown that the adipocytes of guinea pigs are insulin resistant due to a reduced number of glucose carrier proteins.

Studies have also examined the effects of overnutrition on the development of insulin resistance in subjects with normal glucose tolerance. The results thus far indicate that acute overnutrition does play a role in the development of insulin resistance, and that changes in glucose disposal rates are related to in vivo measurements of non-oxidative glucose disposal rates as determined by indirect calorimetry.

Other studies have suggested that muscle glycogen depletion following exercise in animals is associated with increased insulin sensitivity. Studies in man have shown that after exercise, muscle glycogen decreases significantly while muscle glycogen synthase activity

increases significantly, basal and insulin stimulated carbohydrate oxidation rates decrease, and carbohydrate storage rates increase. These results suggest that muscle glycogen synthase activity may be rate limiting for carbohydrate storage rates and therefore for total glucose disposal rates in glycogen depleted men.

Studies continue to attempt to learn more about the mechanisms of action for various hormones and enzymes necessary for metabolism. Gastrin, secretin, cholecystokinin, and bombesin are being studied through in vitro systems while the action of dihydrofolate reductase and its unique molecular biology are being examined in various animal studies.

Clinical research is under way to examine the relationship of nutritional factors to the etiology, morbidity and mortality of metabolic and other diseases or conditions, such as diabetes mellitus, periodontal disease, cystic fibrosis, obesity, hypochloremic metabolic alkalosis, and cystinosis. Clinical studies of the Pima Indians have shown them to have the highest known prevalence and incidence of noninsulin-dependent diabetes mellitus in the world. They also have a high prevalence of obesity, low plasma cholesterol levels, reduced low density lipoprotein (LDL) synthesis, and a decreased incidence of cardiovascular disease. This population appears to be insulin resistant as well as hyperinsulinemic; the hyperinsulinemia found in Pima children is thought to contribute to the development of obesity and diabetes in adulthood. Recently, a study to examine the possible relationship of periodontal and other oral diseases to diabetes in this population has begun. Lipoprotein metabolism in Pima Indians is being investigated in order to further understand the control of lipoprotein metabolism and how lipid metabolism is influenced by obesity and diabetes. Preliminary studies have shown that a large proportion of VLDL is metabolized without conversion to LDL and therefore this alternate pathway might be a mechanism for maintenance of the low LDL levels in this population. Obesity was also associated with an increased flux of free fatty acids without increasing plasma concentrations, which could account for increased VLDL production in these individuals. Total plasma cholesterol and VLDL levels increased with increasing obesity whereas high density lipoprotein (HDL) cholesterol decreased.

It has also been proposed that the high incidence of obesity in the Pima Indians may be due to a thrifty gene, one that would predispose them to store energy more efficiently. It appears that in the obese Pimas, although their basal plasma concentrations of norepinephrine is similar to that of Caucasians, plasma levels are higher following norepinephrine infusions. Thus, they appear to suffer from a clearance defect for norepinephrine as well as a decreased thermogenic response to the hormone following overfeeding. The studies suggest a large flux of substrates and regulators (i.e., insulin) which causes the overproduction of lipoproteins; however, compensatory mechanisms are operative that result in the maintenance of low plasma concentrations.

Two South Pacific populations--the Polynesians of Rarotonga and Melanesians of New Hebrides--are also being studied in terms of differences in lipoprotein metabolism. Data indicate that cholesterol and triglyceride levels in the Rarotongas were higher than those in the Melanesians, and that the Rarotongas have a higher incidence of cardiovascular disease.

In clinical studies of cystic fibrosis (CF), attempts are being made to define more precisely the abnormalities that contribute to the pulmonary and gastrointestinal symptoms of this disease. Lingual lipase activity is being studied in order to further clarify its role in fat absorption in these patients, while serum amylase and its isoenzymes are also being analyzed for diagnostic purposes. The altered fatty acid composition found in the blood and tissue lipids of patients with CF is more often found in those patients with malabsorption problems than in those with normal pancreatic function. Recent studies suggest that the lower caloric intake of the CF patient relative to their caloric requirement may lead to an increased utilization of absorbed essential fatty acids (i.e., linoleic acid).

From studies on the pathogenesis of cystinosis, an inherited disorder characterized by excessive intralysosomal accumulations of the amino acid cystine, it appears that the disorder is due to a defective carrier mechanism required for the escape of L-cystine from the intralysosomal space; this explains the large accumulation of cystine found in this disease.

The evaluation of hypersensitivity reactions after the ingestion of foods continues to be an important research area supported by NIAID. The clinical management of food hypersensitivity (allergy) is complicated by the need for extensive differential diagnosis, the absence of definitive diagnostic procedures, and the lack of satisfactory prophylactic therapy. In general, the approach to the management of food allergy is the same as the approach to the management of allergic diseases of the skin and of the upper and lower respiratory tracts: identification of the offending agent and the treatment of adverse reactions. Results from one study of 45 patients with a history of immediate adverse reactions to foods showed that the majority of the reactions involved the gastrointestinal tract alone or in combination with the skin or respiratory tract, and that the foods most frequently involved were shellfish, peanuts, eggs, fish, tomatoes, and walnuts. The data suggest that an immediate adverse reaction to food may initially present itself in adulthood. These individuals tend to be atopic, usually three or fewer foods are implicated, and sensitivities may persist for years.

Investigations are also under way on the effects of other agents, such as sulfites added to foods as preservatives, on severe asthmatics and individuals with recurrent idiopathic anaphylaxis and systemic mastocytosis. Preliminary data on patients with these diseases who are given increasing amounts of the sulfites suggest that the majority of patients with idiopathic anaphylaxis and systemic mastocytosis are not sensitive to sulfites. However, a subset of severe asthmatics do react adversely to sulfites with increased difficulty in breathing.

Studies carried out as part of the NICHD intramural nutrition program range from research on molecular genetics, inborn errors of metabolism, and endocrinological and reproductive research, to epidemiological research on breast versus bottle feeding. Studies on genetic expression with nutritional deficiencies have shown that with a nutrient imbalance, guanosine 3,5'bipyrophosphate (ppGpp) is involved in the expression of approximately one-half of the E. coli genes, but has no regulatory effects during normal growth. Lethal consequences of the rel S mutation, which abolished ppGpp accumulation during energy starvation, have been observed. The rel A and rel S double mutant is markedly defective in its ability to curtail cellular functions when adapting from luxuriant growth to nutritional impoverishment.

Research continues on various inborn errors of metabolism, including cystinosis, glutathione synthase deficiency, glutathionuria, gamma glutamylcysteine synthase deficiency, homocystinuria, glucose-6-phosphate dehydrogenase deficiency, phenylketonuria, galactosemia, and adrenal leukodystrophy; investigators are particularly interested in developing nutritional therapy and new diagnostic techniques in these conditions. The etiology of cystinosis has been discovered and the first transmembrane lysosomal transport system for amino acids has been identified. The investigator plans to determine which small molecules are carried across the lysosomal membrane and what is the basic defect in lysosomal diseases that involve the storage of free compounds. Currently, treatments of such diseases that are being investigated include using pantethine for cystinosis, betaine for homocystinuria, and cysteamine for type III hyperlipidemia. A clinical trial is examining the safety and efficacy of cysteamine for the treatment of children with nephropathic cystinosis, a metabolic disease that leads to end-stage renal disease before 10 years of age. Cysteamine's effectiveness will be evaluated by determining the creatinine clearance values of the treated children.

The study of obesity in children with Prader-Willi syndrome attempts to detect the anatomic and physiological causes for the lack of the sense of satiety, to establish whether the mechanism involved is the same as in patients with exogenous obesity, to identify any special biochemical or physiological features in these patients, and to determine the pattern of absorption and metabolism of carbohydrates in Prader-Willi patients and those children with exogenous obesity.

Children being treated for glycogen storage disease (GSD) have shown significant improvements in maintaining normal blood glucose levels with the administration of corn starch every 6 hours. These studies also investigate the possible therapeutic effects of glucose, polycose, rice starch, potato starch, cooked corn, cooked potato and cooked rice containing equivalent amounts of complex carbohydrates in maintaining normal blood glucose levels in these patients. The usefulness of starch administration in mollifying and preventing the myopathy of Type III GSD is also being examined.

The use of magnesium in infants with apnea and bradycardia is being investigated since animals deficient in magnesium often develop these symptoms. Magnesium deficiency in animals appears also to manifest itself with retention of magnesium by the kidney. Since rat dams fed 150 mg of magnesium ($MgCO_3$) appear to suffer high fetal wastage, investigators are looking into the effects of feeding dolomite [$CaMg(CO_3)_2$] in these animals. Investigators also are examining the effects of prolonged furosemide administration on magnesium metabolism; changes of bone magnesium and calcium in very young nursing rats with congenital magnesium deficiency; histopathological changes in the lungs of rats with acute magnesium deficiency using light and electron microscopy; the distribution of neurotransmitters by fluorescence microscopy studies; the pathogenesis of the shock-like episode of magnesium deficiency through studies of neurotransmitters release; and differences between congenital and acquired magnesium deficiency in young animals.

Other studies examine the trace elements of sodium and calcium, as well as the use of vitamin supplements. These studies look at the physiological and pathological aspects of the renin angiotensin system with emphasis on the regulation of aldosterone secretion. Specific issues include the regulation of adrenal sensitivity to angiotensin II during altered sodium intake and the mechanisms of steroidogenesis in the adrenal glomerulosa cell. Changes in the kinetics of calcium metabolism in normal children at various stages of growth from infancy to puberty are also under investigation. Another study is examining whether there is a link between vitamin supplements taken in the periconceptional period and the risk of neural tube defects in the infant.

Research on the effects of ethanol on the mother and fetus and on the possible manifestation of fetal alcohol syndrome (FAS) is an important area of nutrition research. Studies that are under way attempt to identify and characterize the biochemical markers in children that may predispose them to alcoholism and/or alcohol-induced dementia in adulthood; to explore the biochemical mechanisms of fetal alcohol syndrome; to develop new methods to treat borderline FAS children in order to improve their postnatal growth and central nervous system retardation; to delineate the effects of a thiamine deficient diet and ethanol on fetal development using an animal model; and to determine the effects of ethanol on various neuropeptides.

Investigators have also shown that changes in thyroid hormones during hypocaloric feeding in humans can now be demonstrated with the use of the pulse wave arrival time (QKd). Data have shown that with prolonged hypocaloric feeding, the QKd is prolonged, and therefore, suggests hypothyroidism at the target organ level. Oral supplementation with T_3 rather than T_4 prevents these changes in QKd. Changes observed in peripheral thyroid hormone levels during hypocaloric feeding appear to be due to adaptive mechanisms that result in hypometabolism.

Results from the study on trends in breast and bottle feeding in Pima women of the Gila River reservation have shown that parity had a positive association with bottle feeding. The highest proportion of bottle feeders occurred among women with small families before 1963 and with large families after 1963. Prenatal and postnatal care had a limited influence on the determinants of breast and bottle feeding. The study shows that mother and infant-oriented reasons dominated in the selection of breast or bottle feeding the first infant; while work-related reasons had a stronger influence on the decisionmaking process for feeding the last child. This study will now determine whether breast feeding or bottle feeding is associated with reduced infections in children.

Another study of 1,275 American mothers, 800 of whom are breast feeders and 475 are bottle feeders, includes examination of independent and joint effects of various factors on the frequency and duration of breast and bottle feeding. These factors include prenatal and postnatal medical services; the mother's perception of support from peers, family and medical environments; confidence, enthusiasm and attitude of the mother toward breast feeding; sociodemographic factors; physiological conditions; and the initial feeding pattern, as well as changes over time.

NEI investigators are examining associations between specific nutrients and normal ocular health and function, as well as various ocular diseases. A new intracellular binding protein for retinoids has been identified in the subretinal space; research continues to elucidate the protein's role in ocular vitamin A metabolism and document its appearance at progressive stages of embryonic and newborn development.

Concentrations of vitamins A and E in the pigmented rat retina and retinal pigment epithelium are known to affect the formation and accumulation of lipofuscin pigment. It was found that the amount of lipofuscin in the retinal pigment epithelium (RPE) is a linear function of the logarithm of dietary vitamin A levels whereas vitamin E deficiency accelerates the accumulation of lipofuscin in RPE, which is identical to the pigment that accumulates with aging. Vitamin A deficiency in rats results in a striking decrease in the amounts of lipofuscin that accumulates in RPE as a result of normal aging or vitamin E deficiency. Scientists are also studying independent changes in lipofuscin associated only with the aging process.

Investigators examine the distribution of calcium, copper and zinc concentrations in the retina, pigmented epithelium, choroid, and biological fluids in animal models of human retinal degeneration and in human retinal diseases. The effects of nutrition and genetic background on the progress of chorioretinal degeneration in the retinal dystrophic pigmented RCS rat are under investigation as well as the etiologies of cataracts and gyrate atrophy. The various etiologies of cataracts being examined include: the distribution of inorganic elements such as copper, zinc, selenium, and calcium in cataracts associated with retinal degeneration; the role of exogenous or endogenous oxidative stress in the formation of cataracts; and

changes in the composition and metabolism of lipids in the plasma membranes and lenses. Inhibitors to the formation of cataracts through the limitation of aldose reductase activity are also being explored. The potential role of aldose reductase and pyrroline-5-carboxylate reductase in cataractogenesis is being investigated. The latter enzyme is involved in the metabolic conversion of ornithine and glutamine to proline, and therefore, may regulate the cellular redox potentials and increase ATP levels through the pentose shunt. Studies of gyrate atrophy attempt to determine how dietary manipulations of pyridoxine administration modify ornithine levels and, in fact, arrest or improve conditions associated with the disease. A study of senile macular degeneration investigates whether the administration of vitamin E and vitamin C protects against vision loss in the good eye of persons suffering from senile macular degeneration in the other eye.

Nutrition as it relates to the aging process is being studied by NIA's intramural scientists in both animal models and human subjects. One area of interest is the mechanism(s) by which undernutrition affects various physiological functions with aging. In one study of male Wistar rats subjected to dietary restriction by alternate days of feeding and fasting, the normal age-associated loss of striatal dopamine receptors in the brain was substantially retarded. For example, the dopamine receptor concentrations in the striata of 24-month-old rats that had been on the restricted diet since weaning were 50 percent greater than those of the control animals of the same age given free access to food. Data collected on the rate of activity of specific enzymes with age support the concept that the rate of aging of most biochemical variables is decreased in those animals with dietary restrictions. However, dietary restriction did not significantly increase the life span of the animals. In fact, in animals aged 17 to 19.5 months a diet providing 50 percent of the RDA for vitamins decreased their life expectancy. Longevity in these animals therefore may be increased by ensuring the ingestion of the RDA for vitamins daily.

Dietary restriction is also being studied in experiments using the monkey Macaca mulatta, in terms of its effects on age-related behavioral changes such as motor performance, thermoregulation, learning, and memory.

Another study is examining the relationship of age to the biological responsiveness of hormones and hormone sensitive tissues. Age-related alterations of beta-adrenergic mediated lipolysis in the rat indicate that the amount and type of fat in the diet affect the hormone sensitive lipolytic response. Dietary fat was shown to have a profound effect on the lipid composition of cell membranes, which in turn controls the activity of numerous cell membrane enzymes including the hormone sensitive adenylate cyclase system.

Dietary fat, however, does not affect every tissue in the same way within the same animal, e.g., a diet high in unsaturated fat has little or no effect on fat cell membranes but greatly affects liver cells, which exhibit an increased hormone responsiveness to both

catecholamines (epinephrine) and the polypeptide hormones (glucagon). In addition, a high fat diet inhibits to a large degree lipolytic responsiveness. The control of lipolysis with age is a complex area of nutrition research and will require further research on the interrelationships of diet and aging.

An important aspect of the NIA intramural program involves human studies under way as part of the Baltimore Longitudinal Study of Aging (BLSA), initiated in 1958 to observe the same subjects over a long period of time in order to quantify true age changes and elucidate the mechanisms underlying these changes. The study group includes 1,000 male and female subjects, ranging from 20 to 96 years of age, who return every 2 years for reevaluation and are enrolled in the study for life. Cohorts from this study population are being examined for changes in bone and skeleton, oral health status, salivary gland function, taste thresholds, plasma lipids, and nutrient intake.

Osteoarthritis, a degenerative joint disease, and bone loss are the two principal age-related changes to the human skeleton. Advanced cases of the former produce severe restrictions of movement associated with pain, while advanced bone loss is likely to result in osteoporosis and frequent bone fractures. Dietary, genetic, and epidemiological factors are being examined in terms of their effects on three skeletal sites--hand-wrist, ulna and radius, and vertebral column--of three different populations, i.e., the participants of the Baltimore Longitudinal Study, a sample of Guamanians (Chamorros), and among patients afflicted with amyotrophic lateral sclerosis/parkinsonism dementia complex of Guam.

Demographic, socioeconomic and dental characteristics are being determined in 254 BLSA participants, who will serve as a basic study population for future cross-sectional and longitudinal investigations of aging and oral health status and function. One study of salivary gland function in BLSA subjects has shown a linear decrease in sodium secretion into the stimulated parotid salivary gland function with age. Males showed a greater decrease than females.

Studies on quality-specific variation in taste thresholds with aging include the detection of taste thresholds for the four basic taste qualities in 81 adults between 23 and 88 years of age. Data indicate that sodium chloride thresholds have a small but significant increase with age; quinine sulfate thresholds have a similar increase but are less significantly related to age; sucrose and citric acid thresholds are not significantly related to age; and citric acid thresholds appear to be different in males and females. Thus, the detection thresholds for the four taste qualities undergo different changes with age.

An analysis of plasma cholesterol values in BLSA participants show that levels increase in early adult life and decrease in late life. All age cohorts showed a significant decline in plasma cholesterol levels between the 1950's and 1970's. The change in body weight, polyunsaturated/saturated fatty acid ratio in the diet, and dietary cholesterol explains only a small percentage of this secular effect.

In order to gain insight on the nutrient intake across the adult age span, 180 BLSA male participants recorded 7-day dietary diaries during three time periods: 1961 to 1965, 1966 to 1970, and 1971 to 1975. At the time of the first dietary diary, their ages ranged from 35 to 74 years. The analysis of the effects of aging, cohort, and time on diet utilized three research designs concurrently--cross-sectional, longitudinal, and time series. The nutrients considered were calories, protein, carbohydrate, fat, saturated fatty acids, polyunsaturated fatty acids, and cholesterol. The data indicate that the intake of calories, fat, saturated fatty acids, and cholesterol decrease with age, while polyunsaturated fatty acid intake increased. Cohort effects were not observed for any of the nutrients.

The Division of Research Services (DRS) provides support to the intramural research efforts of the NIH. Included in these services is a program in laboratory animal nutrition that routinely provides investigators with assistance in matters relating to animal diets. This assistance ranges from providing information regarding the nutrient concentrations of specific diets to direct collaboration in studies where dietary nutrients is the major variable and the formulation of special experimental diets is required. The staff of this program is also involved in monitoring the quality of animal diets purchased for use throughout the NIH. This is accomplished by routinely analyzing diet samples for various nutrient and potential contaminant concentrations.

The laboratory animal nutrition program is responsible for conducting research with the objective of improving the nutritional status of animal species used in research and thus improve the overall quality of animal models. This research has resulted in the development of an open formula diet for each of the animal species used in significant numbers in biomedical research. These open formula diets are not only being used at NIH but also throughout the biomedical research community as standard reference diets. Since the ingredient composition of open formula diets are readily available, the formulations can be altered to produce diets with either deficient or excess nutrient concentrations for programs requiring animal models to study nutrition-related diseases. In addition, open formula diets can be purchased by government agencies via the advertised process. On the average, a 30 percent savings is realized by using this process as compared to procuring diets on a sole source basis. The total savings to NIH research programs resulting from using open formula diets is approximately $150,000 per year.

Areas of research also conducted by the nutrition program include identification of the nutrient requirements of various stocks and strains of rodents, the characterization of animal models and the development of diets for animal species being introduced to biomedical research as new models.

NUTRITION RESEARCH TRAINING

The NIH supports training in biomedical and behavioral nutrition research in both the extramural and the intramural programs. Table IX shows the type and number of persons trained and the expenditures in FY 1983.

TABLE IX

NIH TRAINING IN NUTRITION, FY 1983

Institute	M.D. Degree	Ph.D. Degree	Other Degree*	Pre-Doc	Total Number of Persons Trained	FY 1983 Obligations (in thousands of dollars)
EXTRAMURAL:						
Institute Training Grants						
NCI	12	7	0	6	25	577
NHLBI	26	59	2	49	136	1002
NIDR	1	5	5	1	12	233
NIADDK	6	24	1	36	67	690
NIAID	6	3	0	0	9	9
NIGMS	24	1	1	53	79	273
NICHD	8	5	2	4	19	268
NIA	0	0	0	30	30	4
Subtotal	83	104	11	179	377	3,056
Individual Fellowships						
NHLBI	1	3	0	0	4	55
NIDR	0	1	1	0	2	38
NIADDK	3	7	0	0	10	164
NIAID	2	0	0	0	2	18
NIGMS	1	0	0	0	1	11
NICHD	2	7	0	0	9	69
NEI	1	1	0	0	2	21
NIA	0	1	0	0	1	9
FIC	2	0	1	0	3	7
Subtotal	12	20	2	0	34	392
EXTRAMURAL SUBTOTAL	95	124	13	179	411	3,448
INTRAMURAL						
NHLBI	6	0	0	0	6	52
NIADDK	5	4	0	0	9	311
NICHD	11	14	7	0	32	321
INTRAMURAL SUBTOTAL	22	18	7	0	47	684
NIH TRAINING TOTAL	117	142	20	179	458	4,132

* Other Degree includes M.D./Ph.D, Ph.D./D.D.S., D.D.S, D.V.M., D.Sc., etc.

Extramural Training

Within the extramural program, two basic mechanisms are used for nutrition training support: institutional awards and individual awards.

The institutional national research service awards, commonly called "training grants," are designed to enable institutions to make training awards to individuals selected by them for predoctoral and postdoctoral research training. In FY 1983, out of the total NIH expenditure of $135,152,000 to train 8,963 full-time equivalent persons, $3,056,000 was expended to train 377 persons in nutrition. Thus, nutrition training accounted for 2.3 percent of the total NIH training expenditure and 4.2 percent of the total trainees supported.

The postdoctoral individual national research service awards, called "fellowships," are awarded to provide postdoctoral research training to individuals to broaden their scientific background and extend their potential for research. Out of the total NIH expenditure of $29,502,000 to support 1,607 fellows in FY 1983, the nutrition program expended $391,000 to support 34 fellows. Thus, nutrition fellowships accounted for 1.3 percent of the total NIH expenditure for fellowships and 2.1 percent of the total NIH supported fellows.

Combining training grants and fellowships, $3,447,000 was expended to support the 411 persons trained in nutrition in FY 1983. The nutrition expenditure accounted for 2.1 percent of the total NIH training expenditure and the number of trainees in nutrition accounted for 4.0 percent of the total NIH trainees.

Table X shows that whereas the number of trainees and the financial support for NIH as a whole remained relatively constant from 1978 through 1983, the number of trainees in the nutrition program doubled between 1978 and 1979, remained relatively constant until 1982, and has since increased slowly. As can be seen over the 6-year period, the number of nutrition trainees reached its highest level yet in FY 1983, with 377 trainees.

Despite the fact that total NIH fellowships have seen a slight increase in FY 1983, the number of nutrition fellowships has continued to decrease.

TABLE X

COMPARISON OF TOTAL NIH AND NUTRITION PROGRAM SUPPORT OF EXTRAMURAL RESEARCH TRAINING AND FELLOWSHIPS, FY 1978 - FY 1983
(in thousands of dollars)

	Total NIH				Nutrition Program			
	Training		Fellowships		Training		Fellowships	
FY	Number of Trainees	$	Number of Fellows	$	Number of Trainees	$	Number of Fellows	$
Year								
1978	9,260	117,581	1,863	26,345	130	1,956	39	463
1979	9,204	116,193	1,993	27,468	261	2,555	36	466
1980	8,878	141,719	1,786	34,669	284	3,201	51	628
1981	9,121	144,719	1,574	30,897	268	3,159	36	549
1982	8,867	123,407	1,539	27,067	307	2,419	38	415
1983	8,963	135,152	1,607	29,502	377	3,056	34	391

Examples of areas in which the trainees carried out their work include the following:

- o Nutrition and metabolism
- o Experimental and clinical nutrition
- o Clinical nutrition for physicians
- o Graduate training in nutrition
- o Development of time budgeting, energetic constraints
- o Role of thermogenesis in body weight regulation
- o Control of food intake: focus on nutrition and behavior
- o The influence of gastrointestinal signals on satiety
- o Nutrition and nephrology
- o Protein, amino acid, and urea metabolism in humans
- o Mechanisms of protective effect of dietary protein
- o Function of protein S, a new vitamin K-dependent protein
- o Differentiation of proteins in cultured mesothelium
- o Infectious diseases/basic microbiological mechanisms
- o Human interferon deficiencies in pediatric patients
- o Carcinogenesis and drug development
- o Multidisciplinary oncobiology
- o Nutrition and oncology: prevention and intervention
- o Experimental oncology and nutrition
- o Sympathetic regulation of fat metabolism during sepsis
- o Research in burns and trauma
- o Nutrition metabolism with trauma
- o Multidisciplinary heart and vascular disease research

- o Plasma lipoproteins and apoproteins
- o Nutrition-behavioral cardiovascular disease prevention
- o Interdisciplinary training program in lung disease
- o Postdoctoral training in lipid research
- o Nutrition, lipid metabolism, arteriosclerosis, and atherosclerosis
- o Lipid, lipoproteins, and atherosclerosis
- o Genetics of atherosclerosis
- o Characterization of postprandial lipoproteins
- o Dietary fat in lung microvascular injury from oxygen
- o Lipoprotein methodology, structure, and function
- o Chemistry of lipoproteins and atherosclerotic lesions
- o Cardiovascular epidemiology, biostatistics, and nutrition
- o Cardiovascular disease prevention
- o Cardiovascular pathology
- o Cardiovascular pathophysiology and biochemistry
- o The role of the liver in cholesterol ester metabolism
- o Target organ insensitivity to $1,25\text{-}(OH)^2\text{-}D_3$
- o Metabolism of $1,25\text{-}(OH)^2\text{-}D_3$
- o Regulation of $25\text{-}(OH)^2\text{-}D_3\text{-}1\text{-}$hydroxylase
- o Vitamin D metabolism during pregnancy and lactation
- o Intestinal absorption and metabolism of riboflavin
- o Biotin: the mechanism of carboxylation
- o Maternal nutritional status and plasma volume expansion
- o Thermal aspects of maternal care in deermice
- o Nutrition and perinatal biology
- o Nutrition and growth and development
- o Training in neonatal biology
- o Cultural and environmental factors affecting child malnutrition: Sudest Island Region, New Guinea
- o Fatty acids as an energy source in pregnancy and in the neonate
- o The role of biological rhythms in reproductive behaviors, cellular growth, and differentiation related to the biology of the neonate
- o The interrelationships between body metabolism and puberty
- o Nutrition and oral health
- o Effect of high levels of fluoride on developing tooth enamel
- o The role of pigment epithelium in supplying phospholipids or their precursors, including fatty acids to retinal photoreceptor cells
- o The role of zinc and vitamin A deficiencies independently and together in the development of the structure and function of the fetal retina and the level of retinal vitamin A
- o Vitamin A and epithelium glycoprotein synthesis
- o Vitamin A status at various gestational ages
- o Mediation of endotoxin effects on zinc and copper metabolism
- o Effect of fluoride and calcium++ on amylase secretion

Intramural Training

Within the NIH intramural program, three Institutes, NHLBI, NIADDK, and NICHD, supported training of 47 scientists at an obligation of $684,000 in FY 1983.

The intramural trainees worked in the following areas:

- o Starch metabolism in patients with glycogen storage disease
- o Basic chemical defect in cystinosis in order to develop new and improved methods of treatment and diagnosis
- o Development and evaluation of better means of diagnosis and treatments for the inborn errors of metabolism
- o The kinetics of calcium metabolism in normal prepubertal children and the evaluation of disease-related changes in calcium metabolism in both children and adults
- o Effects of a thiamine deficient diet and ethanol on fetal development in an animal model
- o Role of magnesium in fetal and postnatal maturation, and in the treatment of infants with apnea
- o Pathophysiology of fibrodysplasia ossificans progressive and therapeutic intervention with 13-cis retinoic acid
- o Nutrition induced alterations in metabolism
- o Control of macromolecular synthesis during normal growth as well as nutritional deficiency
- o Renin-angiotensin system and aldosterone regulation
- o Biochemical studies of hepatic and intestinal function
- o The anatomic and physiological causes of the absence of satiety in Prader-Willi syndrome
- o Pathophysiology of the adipocyte in human obesity
- o Effect of overfeeding on glucose disposal
- o Insulin regulation of glucose transport and metabolism
- o Hormonal regulation of cellular metabolism in order to define the defect in glycogen metabolism resulting from diabetes and to elucidate the mechanism of action of insulin
- o Diabetes and other chronic diseases in U.S. Indians
- o Lipoprotein metabolism in Pima Indians
- o Vitamin D resistance and related disorders.

The areas of nutrition research presented in this section of the report reflect those areas where significant advances have been made over the past year. They include studies on the role of nutrition in the the early development of the CNS, particularly the brain; the effects of alcohol consumption on fetal development; the influence of nutrition on the aging processes; the role of dietary fiber in health promotion and disease prevention; the development of reliable methods for the assessment of nutritional status; the etiology, treatment and prevention of obesity as well as its role as an independent risk factor for cardiovascular disease; nutrition and behavior; the relationship of plasma cholesterol levels to the pathogenesis of coronary heart disease; the role of nutritional therapy in the control of diabetes; food allergies; nutrient deficiencies and excesses found in CNS disorders of amyothrophic lateral sclerosis and parkinsonism-dementia; the role of diet in the development of dental caries; total parenteral and enteral nutrition; and the effects of food-borne contaminants and additives on biological systems.

Studies on the role of nutrition in central nervous system development includes research on nutrition and early development, particularly brain development. Some studies are examining the hypothesis that several pathways of brain metabolism in the developing animal are linked to nutrient availability in the brain. Such studies attempt to quantitate developmental changes of both blood-brain transport and brain metabolism of amino acids. This research will increase our knowledge as to whether such amino acids as choline, ornithine, and adenosine are essential to the developing brain and provide the necessary rationale for monitoring plasma levels of such nutrients in the fetus.

Additional studies examine undernutrition and its effect on the plasma membranes of synaptic nerves in the brain. Investigations have demonstrated that offspring of undernourished rats have a decreased concentration of protein and changes in the synthesis of gangliosides, glycoproteins, and other specific proteins in the synaptic plasma membranes. This decrease in protein concentration may precipitate the synaptic abnormalities observed in these animals.

Other investigations on the effect of diet on brain neurons, particularly the synthesis and release of serotonin by brain neurons have examined the effects on the sleep patterns of newborn infants of variations in diet designed to affect tryptophan availability. It is known that the synthesis and release of serotonin by brain neurons is proportional to the availability in the brain of its precursor, tryptophan. The brain tryptophan concentration is influenced by dietary intake of tryptophan and other large neutral amino acids (valine, leucine, isoleucine, tyrosine, methionine, and phenylalanine) that compete with tryptophan for transport across the blood brain barrier, as well as the intake of carbohydrate and associated insulin secretion.

The 20 healthy newborns included in the study were given tryptophan in a 10 percent glucose solution, or valine in a 5 percent glucose solution. The tryptophan formula was chosen to maximize the transport of tryptophan across the blood brain barrier, whereas the valine solution minimized tryptophan transport.

The sleep patterns of the two groups of infants fed tryptophan or valine were compared to the sleep patterns observed after routine formula (Similac). The infants fed tryptophan entered active sleep 14.1 minutes sooner than after Similac, and entered quiet sleep 20 minutes sooner. Those infants fed valine entered active sleep 15.8 minutes later than when fed Similac, and entered quiet sleep 39 minutes later.

Data from this research demonstrate that modifications of the preparations fed to newborns can influence the length of time it takes the newborn to fall asleep after a feeding. It is believed that the changes observed in sleep behavior could have been caused by changes in brain tryptophan and subsequent serotonin synthesis and the neurotransmission within the newborn's brain.

Alcohol consumption affects health, and at no other time is the effect of alcohol consumption more dramatic than during fetal development. In order to better understand the effect of alcohol consumption during pregnancy on the proper development of the fetus, an animal model of pigtailed macaques has been developed to determine the levels of binge alcohol consumption that can produce defects in infants of mothers who drink during pregnancy. Early results of research using this animal model indicate that six cocktails consumed once a week by the mothers may cause serious problems in newborns. Once a week, pregnant pigtailed macaques were given either a high dose of ethanol, equivalent to a binge of 10 cocktails in humans, or a moderate dose equivalent to 6 cocktails or a 6-pack of beer. The animals received these doses beginning at 40 days after conception until the end of term. The animal receiving the high dose of ethanol produced an infant with facial abnormalities and mental retardation similar to those seen in human fetal alcohol syndrome (FAS). Of the three animals receiving the moderate doses of alcohol, one had a miscarriage, one gave birth to a retarded infant, and one produced an infant which had signs of FAS.

The study revealed several important similarities of the retarded animals to children with FAS, i.e., neurological defects were apparent, nerve tissue in the cerebral cortex was inadequately developed, facial features were adversely affected, and significant changes in brain receptor activity were observed. The brain of the high dose infant was small and grossly misshapen, which is also apparent with human newborns with FAS. This animal was so severely retarded that it required 5 times as long to develop behavioral patterns normally observed within 22 days of birth.

Differences between animal and human FAS appeared in weight gain and skeletal growth. Although human infants with FAS are abnormally small, the neurologically retarded monkeys were heavier than average

and the male moderate-dose offspring was also taller than normal. The animals did not have any major malformations in the skeleton, heart or kidneys, although such malformations occur in human FAS patients. Even though no particular species can perfectly model the human, the macaque is preferable to previous FAS models because primate metabolism and fetal growth patterns are closer to humans than other mammalian forms. Additional research in this area is examining the time when drinking during pregnancy causes the most damage. Studies suggest that brain development can be severely altered by fetal exposure to alcohol even beyond the first trimester.

Much of the research on nutrition and aging considers whether nutritional needs change significantly beyond the middle decades of life and, if so, how these needs change and what specific nutrients are involved. The study of human aging in terms of the genetic and other environmental factors that influence morbidity and mortality is an important area of research. Nutrition and diet are certainly among the most influential environmental factors to exert chronic influence on the aging organism.

Laboratory and clinical studies are under way to examine the effect of aging on nutrient requirements, absorption and metabolism, as well as the effect of diet on the natural history of diseases common in the elderly such as osteoporosis, diabetes, blindness, cancer, hypertension and atherosclerosis.

A 5-year study of 72 pigtailed macaques examines the possible interaction of nutrition--specifically, the U.S. diet with its high proportions of fat, cholesterol, simple sugars, and sodium--and normal biological aging processes that might produce the physiological and behavioral changes and diseases found in the elderly. One group of 36 monkeys follows the U.S diet while a matched group follows the alternative diet. The U.S. diet, which is analogous to the one followed by the average American, has six times the amount of cholesterol, four times the amount of salt, and twice the amount of sugar as the "alternative more healthy diet." Neither diet contains alcohol, caffeine or common food additives such as preservatives. Each group of monkeys includes an equal number of males and females ranging in age from 4 to 25 years, a span equivalent to 12 to 75 years in the human. Animals of various ages and sexes are housed in group cages to allow for normal social interactions.

Periodic examinations provide information on 48 standard biological and clinical characteristics and four measures of biological aging. The studies are designed to clarify the effects of biological aging and diet on carbohydrate and fat metabolism, psychological functions, pharmacodynamics, genetic assurance mechanisms, and several specific disease processes such as periodontal and degenerative bone disorders, atherosclerosis, and preneoplastic mammary dysplasia. Twenty collaborating investigators across the country are analyzing blood samples and biopsy specimens in an attempt to clarify the effects of aging and diet on metabolism, vision, and cell function.

This study is designed to answer some of the questions as to how diet interacts with the biology of aging in the pigtailed macaque, since previous studies have identified changes in behavior, mental function, anatomy and physiology that accompany aging in these animals. For example, in one 2-year study the oldest animals appeared to have learning deficiencies, lower levels of certain neurotransmitters in the brain, thinner capillary walls in the brain cortex, thick coronary vessels, a decrease in the number of alveoli and air space in the lungs, as well as a decrease in bone mass and menopause. Thus, this study may identify diet-related problems in these animals that are similar to problems that occur in man.

A prospective study is under way to examine the nutritional status of the elderly with investigators analyzing the relationships between nutrient intakes and their blood levels, and between borderline deficiencies of specific nutrients and intellectual functioning. Previous work by investigators has pointed to impaired peripheral tissue sensitivity to insulin as the primary factor responsible for the decrease in glucose tolerance observed with advancing age. It is hypothesized that the abnormal glucose tolerance observed in the elderly is due to a reduced responsiveness of adipocytes to the antilipolytic effects of insulin. The theory behind this concept is that free fatty acids released from adipose tissue or end products of free fatty acid metabolism inhibit glucose utilization. These investigators wish to determine if insulin is as effective in the elderly as in younger controls in reducing the release of free fatty acids from adipose tissue after a glucose challenge. Various studies are designed to determine the response of whole body glucose, free fatty acids and glycerol kinetics to various stimuli, including insulin, norepinephrine, mild physical exercise, and varying nutritional status.

Over the past few years, claims have been made that dietary fiber has a number of beneficial effects on health. The therapeutic effects include the relief of constipation, the symptomatology of diverticula disease and the recent indication of its role in controlling glucose tolerance in diabetics. In addition, the prophylactic effects of dietary fiber are now being considered, e.g., studies are under way to closely examine the suggestion of an inverse correlation between the intake of dietary fiber and the incidence of colon cancer.

In 1977, the NCC held a workshop entitled, "The Role of Dietary Fiber in Health," to address this issue. A plenary session covered the state-of-the-art in dietary fiber research; i.e., its historical aspects, definitions, interactions with bacteria, and its relation to digestive tract infection and the specific disorders of obesity, diabetes, cancer and arteriosclerosis. Six working groups covered such topics as the analysis of the various components of fiber found in foods; fiber's effects on the function as well as on the development of diseases of the gastrointestinal tract; the role of dietary fiber in cholesterol and bile acid metabolism as well as the relationship between the amount and type of fiber on lipid metabolism and heart disease; fiber's role in preventing carcinogen formation through the absorption of sterols or other potential and actual

carcinogens or on the metabolism of sterols and toxins by bacteria; and the effects of dietary fiber on total food intake through mechanisms such as dietary dilution and distention of the intestinal wall. As a result of the workshop a number of studies further explored the aforementioned areas of interest.

In 1980, based on the research data available, the importance of including adequate amounts of fiber in one's diet was emphasized by DHHS and USDA in the publication, Nutrition and Your Health--Dietary Guidelines for Americans.

In FY 1983, research studies examined the interactions between plant fibers such as wheat bran, pectin, and cellulose with the digestive enzymes pepsin, trypsin, chymotrypsin, and lipase; as well as the possible role of fiber in the development and/or alteration of the metabolism of intestinal bacteria by enzymes and metabolites, and fiber's effects on the bioavailability of nutrients such as zinc, B_{12}, folacin and other vitamins.

Studies with animal models have shown that different fiber fractions have specific effects on intestinal transit time, lipid absorption and metabolism. Gelling fibers inhibit fat absorption, particularly the accumulation of lipid in the cell, and play a role in the cytokinetics and mucin production of the intestine that result in morphological changes of the intestine. These parameters are generally considered to be significant factors contributing to the incidence of cancer.

A number of studies are examining the role of fiber in the development of cancers of the colon, breast, stomach, etc., in men and women, as well as in special population groups such as the Seventh Day Adventists and Japanese immigrants. Several chemical and physiochemical properties of dietary fibers, such as its water-holding and bulking capacity and its effects on the dilution of carcinogenic secondary bile acids, have been suggested as factors important for the reduction of colon cancer incidence.

Recent work has also shown that dietary fiber influences muscosal growth and cell proliferation in the intestine. Dietary fibers may also produce acidification of colonic contents, which in turn influences colonic metabolism and function. Studies test the hypothesis that the risk for colon cancer is associated with specific qualitative and quantitative parameters in fecal bile acid patterns and with fecal mutagens which reflect dietary fat and fiber intake.

Metabolic studies also consider the effect of fiber on hormone levels, blood components as well as fecal steroids. For example, one study is investigating the effects of different diets, e.g., fiber free or supplements of 20 percent wheat bran, 20 percent oat bran, 10 percent pectin or 10 percent guar gum, on tumor induction rates and intestinal epithelial cell cytokinetics in terms of tumor development in rats given the carcinogen 1, 2-dimethylhydrazine (DMH). The effects of fecal pH on tumor induction with DMH will also be investigated by feeding a nonabsorbable carbohydrate, lactulose or sorbitol, which produces acidification of the large bowel contents.

Other studies are under way to examine the impact of dietary fiber on several additional neoplastic models, such as aflatoxin-induced liver hepatomas, the walker carcinoma 256 cell line and the lymphoid L1210 line. The carcinogenic processes considered in such studies include chemical carcinogen metabolism, cocarcinogenesis and promotional phases of neoplastic cell evolution and growth, carcinogen sequestration in the gastrointestinal tract and immunocompetence capacity as related to carcinogen exposure and subsequent neoplastic cell growth.

The effect of fiber on maintaining the body's balance of selenium, copper, cadmium and zinc levels in relation to carcinogenesis is also being studied. Lignins are one type of fiber under investigation since they are thought to influence carcinogenesis through their ability to bind several carcinogens and cocarcinogens, particularly nitrosamines and bile salts, and their oxidation-reduction properties.

Historically, identifying the various kinds and amounts of fiber, i.e., bran, gums, pectins, cellulose, hemicellulose, etc. in particular foods was determined using the crude fiber method--a method that provides purely erratic fiber values. Methodology has advanced somewhat today with fiber values obtained by the Southgate procedure; the Van Soest neutral and acid detergent procedures; and the Crampton and Maynard cellulose methods. Establishing the best method for the analysis of the fiber content of various foods remains a major research agenda.

In terms of future research in the area of fiber and cancer, new or improved methodologies for the determination of total dietary fiber and the separation, identification and quantitation of different fiber fractions are needed since data on total dietary fiber (including cellulose, hemicellulose, pectic substances, gums, mucilages, modified cellulose and lignin) and dietary fiber fractions present in the U.S. food supply are lacking. The abscence of this analytical data seriously impedes the elucidation of the significance of these dietary components to the incidence of cancer.

In addition, clinical trials will examine the effect of micro and macronutrients on cancer risks in humans, and fiber is one of the dietary components that will be considered in terms of its effects on carcinogenesis.

Research on nutritional status assessment includes investigations to develop and evaluate various methods useful to determine the requirements of essential nutrients throughout the life cycle from fetal life to infancy, childhood, adolescence, adulthood, and the aged. The quest to determine easy ways to determine nutritional status continues. Studies carried out in both normal and patient populations examine biochemical, anthropometric, maturational, and functional indices of nutritional status; methods to measure nutrient concentrations in various tissues and plasma; and dietary recall methods. NIH is the major agency that supports research for the development of methods used in nutrition surveys.

Reliable methods for assessment of nutritional status are needed in order to: (1) determine whether or not impairment of health is the result of inadequate or inappropriate diet; (2) establish the specific nature of any nutritional problem underlying such health impairment; (3) provide knowledge on which to base dietary treatments for improving health; and (4) permit evaluation of the effectiveness of nutritional treatments or interventions that may be undertaken to improve health.

Methods to assess nutritional status include anthropometric measurements of weight and height, and skinfold thicknesses; biochemical measurements including assays for serum and tissue levels of various vitamins, minerals, fatty acids and amino acids; balance studies to assess bioavailability, absorption and metabolic status of trace elements, etc.

Research studies to examine the value of using hair analysis as a method for assessing nutritional status have shown it to be worthless for detecting vitamin deficiencies and of very limited value for estimating the body's mineral status or trace element deficiencies. Some of the major problems with the interpretation of hair analysis data include: the lack of information on the correlation between hair concentrations of various elements and levels in the tissues and body fluids; the lack of data on the normal range of trace element concentrations in hair; the possible contamination of human hair with minerals from the environment; the findings of greater concentrations of certain elements, such as copper, at increasing distances of the hair from the scalp indicating exogenous elements in the sample; and alterations in the concentrations of trace elements in the hair as a result of various hair treatments such as bleaching, dyeing, permanent waves, and even shampooing. Another factor that must be considered in hair analysis is the hair growth rate. For example, hair growth is slowed in individuals with severe zinc deficiency although the zinc content may be normal, whereas in those individuals with mild zinc deficiency the growth rate appears unaffected but hair zinc is markedly decreased. Also, the concentrations of some elements in the hair appear to vary according to sex, age and season of the year. Data from hair analysis, at present, are to be considered uninterpretable.

Obesity is a major health problem in the U.S., affecting both children and adults. Data from the National Health and Nutrition Examination Survey I (NHANES I-1971 to 1974) show that overweight affects a significant proportion of our population; 14 percent of the men and 24 percent of the women between the ages of 20 to 74 years were found to be 20 percent or more above their desirable weight. One of every three women past the age of 55 is overweight. Similarly, data from the second NHANES (1976 to 1980) indicate that the prevalence of obesity persists and that those in the 90th percentile are even heavier than in previous surveys. These figures on obesity were obtained using the average weights of NHANES participants between 20-29 years of age as a standard. If however the Metropolitan Relative Weight (MRW) is used as the standard to define the percent of

men and women who are at an elvated risk for increased mortality (MRW > 110 percent or a body mass index (BMI) of 24.4 kg/m^2), the latest data from the Framingham Heart Study show that these percentages rise to 80 percent for the men over the age of 40 years and to about 70 percent for the women.

Obesity is associated with hypertension, hyperlipidemia and hypercholesterolemia, and diabetes, and contributes to increased postsurgical infections and complications of pregnancy. In women, obesity is associated with increased risk for cancer of the breast and endometrium. It has recently been shown to be an independent risk factor for CVD with cigarette smoking exerting a separate effect from that of overweight. Consequently, research on the biomedical and behavioral aspects of obesity is an important area of consideration at the NIH.

Research is under way to examine the genetic, metabolic, clinical, environmental and behavioral aspects of obesity in humans and in animal models; to define the types of obesity; and to establish better methods of prevention and treatment. Studies of the developmental aspects of obesity, its natural history, and its heterogeneous origins attempt to identify determinants of obesity in infancy, childhood and adolescence.

One study which examined the relationship between the degree of obesity and the incidence of CVD included approximately 5,000 subjects of the original Framingham Heart Study cohort who were followed for 26 years for the development of CVD. Data from the study indicate that the risk of CVD increased in both men and women with increasing Metropolitan Relative Weight[1] at the time of entry to the study.

The degree of obesity in both men and women appeared to be an important long-term predictor of CVD incidence, particularly among the younger members. The association of weight to CVD incidence was most pronounced in those younger than 50 years. The incidence of coronary disease, the most frequent manifestation of CVD, increased with increasing MRW and the gradient of risk was steeper in younger men and women. Obesity in both sexes did not exert its influence solely through its association with other coexisting risk factors for CVD, but predisposed individuals to premature CVD.

In addition to the relationship observed between MRW to disease risk, the change in MRW after the young adult years also made an independent contribution to the prediction of CVD. At any level of MRW at age 25 years, weight change was positively and significantly associ-

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[1] The midpoint of the desirable weight range for medium frame (Metropolitan Life, 1959 Table) was chosen as the reference weight for a given height. The MRW was computed for each subject by forming the ratio of her or her body weight to the reference weight for the particular height. This ratio is expressed as a whole number in percent.

ated with CVD risk in both sexes with a stronger relationship observed in men. These results illustrate not only the detrimental effects of weight gain, but also the benefits of weight reduction in obesity. The study also suggests that men may be more generally sensitive than women to the effects of weight changes, because its impact on disease could not be attributed solely to other risk factors. The duration of obesity is also an important consideration in terms of the incidence of CVD.

Thus, this study points out that leanness and avoidance of weight gain before middle age are advisable goals in the prevention of CVD for most American men and women. In addition, intervention on the well-established risk factors for disease should be accompanied by weight loss in the overweight individual. This study refutes the previously held consensus that the increased risk for cardiovascular disease among heavier individuals is due primarily to the influence of the associated risk factor profile and not to the degree of obesity per se.

It has been apparent since publication of the early results of the Framingham Heart Study that the relationship between relative body weight and total mortality is complex. Another report of the Framingham Heart Study participants examined the relationship between obesity and long-term mortality, after controlling for the strong inverse association between weight and cigarette smoking and the noticeably elevated mortality among lean cigarette smokers. This study examined cigarette smoking as a confounder of the relationship between relative weight and long-term mortality.

The MRW was calculated for each participant at the time of entry to the study. Findings from this study suggest that elevated mortality in low weight American men results from the mortality risks associated with cigarette smoking, and demonstrates the need to control for cigarette smoking when considering the relationship between relative weight and mortality. This study validates the concept of "desirable weight" developed by the Metropolitan Life Insurance Company in 1959, since when smoking was controlled even those men who were of average weight (about 20 percent above desirable weight) showed appreciably elevated mortality due to all causes.

According to the results of this study, "one can not make inferences about the mortality outcomes of less-than-desirable weight men who have not been exposed to tobacco because they do not exist in sufficient numbers in this sample. The almost complete confounding of leanness and cigarette smoking observed in Framingham men may also exist in most studies of American men that have been reported in the last twenty years. It would appear that as long as this extensive confounding between cigarette smoking and leanness exists, caution will need to be used in interpreting the results of studies that attempt to estimate the relationship between mortality and levels of relative weight without taking smoking into account."

The motivating forces controlling food selection and food intake are diverse. The physiological factors of taste, smell, gastric and

humoral responses to certain foods are often influenced by social, cultural and religious values, as well as by learned habitual behaviors. Studies on nutrition and behavior attempt to define the exact role of these values and behaviors in influencing food preferences and aversions, as well as define the influence of dietary intake on subsequent behavior.

Studies on nutrition and behavior have also examined the etiology of obesity and its treatment; i.e., the influence of environmental or social factors on eating patterns that lead to obesity have been examined, along with various behavioral approaches to the possible prevention and treatment of obesity.

One important study in this area examined the relationship of parental weight to weight change and behavioral and physiological risk factors in obese preadolescents. It is known that one of the major contributing factors to childhood obesity is the weight of the parents, and that children with two obese parents have two to three times the amount of fat as do children with two lean parents. Furthermore, children with heavy parents are more likely to become obese than are children with lean parents. The purpose of the study was to define the role of parental weight in the child's weight loss. For the study, 36 obese children were stratified into either the thin parent group (17 children), or heavy parent group (19 children with at least one obese parent), and treated for 1 year. The children and overweight parents were put on a 1,200 calorie diet along with a lifestyle exercise program.

Results from this study indicate that for the first 6 months changes in weight were similar for children with thin or heavy parents. At the end of 1 year, however, children with thin parents were 5 pounds lighter while children with one heavy parent were 1.2 pounds heavier, and those with two heavy parents were 5.7 pounds heavier. It is interesting that while heavy parents lost more than thin parents, children with thin parents lost more weight than children with heavy parents. In terms of child fitness and behavior patterns as a function of parental weight, children with heavy parents were significantly less fit and more withdrawn than children with thin parents. Given that obese parents may be withdrawn, parental behavior must be considered as likely a causal agent for childhood depression as childhood overweight. The data also suggest that child blood pressure levels and change are likely to be a function of parental blood pressure levels and not parental weight categories.

Thus, this study provided information on the role of heavy parents in determining the effect of treatment for their children and on the interaction of child and parent weight in determining physiological and behavioral risk factors for obese children. It clearly points out that weight loss in children is affected by parental weight. Other factors that can affect weight change include genetic makeup, developmental differences in energy balance, and behavioral factors. The interrelationship between the physiological, behavioral, and cognitive variables needs to be examined further in order to understand the etiology and consequences of obesity and related risk factors.

Another study is comparing the efficacy of two liquid diets in a weight reduction program; one formula contains long-chain triglycerides while the other contains medium-chain triglycerides. The postulate being tested is that the medium-chain preparation provides a greater degree of satiety and will therefore result in a greater weight loss. Other investigators are examing the effect of 30 mg. of d-fenfluramine, a serotoninergic agent, on meal and snack intakes of protein and carbohydrate foods in obese subjects. Twenty to thirty obese subjects who claim to have excessive appetites for carbohydrates are being treated with 15 mg d-fenfluramine (and alternately placebo) twice a day during two 8-day treatment periods. Subjects are allowed to choose freely from among three protein-rich and three carbohydrate-rich isocaloric food choices at each meal. Between meals, subjects are allowed to choose at will from among five protein-rich and five carbohydrate-rich isocaloric snack choices provided via a vending machine; their choices are recorded automatically by a computer. Data on 13 subjects demonstrate that in 11 subjects taking d-fenfluramine, carbohydrate intake decreased significantly and protein intake remained constant. These observations suggest that d-fenfluramine can selectively inhibit carbohydrate intake. Other investigators have added phentermine in combination with fenfluramine to alleviate the side-effects of fenfluramine.

The behavioral approach to the treatment of obesity has also included research on the effectiveness of monetary contracts in promoting weight loss and maintenance. Participants in two studies to examine the utility of monetary contracts for weight loss attended weekly group sessions directed by health professionals trained in nutrition, psychology and health education, and each received an individualized diet and exercise program. The contracts used required participants to deposit money in advance and the money was refunded contingent on predetermined increments of weight loss. Contracts varied in terms of contract size ($1, $5, or $10 per pound of weight loss), and individualized versus those based on average group performance. Contracts of similar monetary amounts were compared in terms of differences in the distribution of refunds across time, i.e., contracts with constant increments for each pound lost were compared with increasing increments for weight lost (i.e, the later weight losses were rewarded more heavily).

Findings from this study indicate that monetary contracts are well received and reliably increase short-term weight losses in both men and women from various populations by 30 to 40 percent above similar weight loss programs without incentives. Contract size was shown to be positively related to weight loss, with individuals having a $300 contract losing more weight after 15 weeks than those individuals having either a $30 or $150 contract. Individuals enrolled in a group contract lost more weight than those having individualized contracts. Increasing refund schedules produced larger short-term losses than a constant refund schedule. These studies have only focused on short-term effects with no maintenance support provided to patients beyond the end of the 15-week contract. Current data suggest that without maintenance supports, weight losses observed with

contracts return quickly to levels similar to those observed in studies without contracts. Studies currently under way are examining the usefulness of contracts in weight maintenance as well as those that do not require a large lump sum monetary outlay.

Additional research on nutrition and behavior has examined the specific effect of estrogen on eating behavior in primates. Studies have confirmed that when estrogen levels are high, such as just before ovulation or during pregnancy, food intake by female rhesus monkeys decreases. Data indicate that 10 of 12 monkeys studied during a total of 55 menstrual cycles consistently ate less food before than after ovulation. The most noticeable drop in food intake occurred during the 3 to 5 days before ovulation when estrogen levels peaked. For all 12 animals, food intake during this preovulatory phase averaged about 30 percent lower than during the midluteal phase, and in some animals about 50 percent lower. Human studies have also suggested a relationship between estrogen levels and food consumption.

In terms of pregnant animals, food intake dropped dramatically in eight tested pregnant rhesus monkeys during the latter part of the first trimester--the period of morning sickness in humans thought to be provoked by high estrogen levels. A reduced appetite continued through the third trimester. After birth, however, when estrogen levels dropped, food intake increased.

This result was tested further in eight monkeys without ovaries which received time-released capsules of estrogen and progesterone. With the release of the same levels of estrogen present at ovulation, the appetite fell to 16 to 56 percent of the animal's normal intake. Progesterone release had no effect on eating patterns.

It is hypothesized that estrogen is transported into the hypothalamic cells of the brain where it induces protein synthesis and alters the body's "set point" for energy regulation. Estrogen may also affect energy metabolism through its effect on the liver, pancreas, and fat cells. The decreased food intake associated with estrogen levels, however, does not lead to weight loss because energy metabolism becomes more efficient. The increased efficiency in energy metabolism with high estrogen levels was evident from the 15 percent increase in the total weight of the mother and fetus even though food intake remained at or below prepregnancy levels.

Coronary heart disease (CHD) remains the major cause of death and disability in the U.S. and in other industrialized countries despite declines in CHD mortality rates. Nationally, more than 1 million heart attacks occur each year and more than a half million people die as a result. Epidemiological studies have established that the higher the plasma total or low density lipoprotein cholesterol (LDLc) level, the greater the risk that CHD will develop. Dietary cholesterol and saturated fats contribute to an elevated blood cholesterol level which in turn is related to an increased rate of heart attacks particularly in those patients with Type II hyperlipoproteinemia. It is also known that plasma total and LDLc may be reduced by diet and drugs.

The Lipid Research Clinics-Coronary Primary Prevention Trial was undertaken by the NHLBI to answer the important question of whether or not the lowering of plasma cholesterol in hypercholesterolemic men would reduce their risk of developing CHD. In 12 participating clinics, a total of 3,806 asymptomatic middle-age men with primary hypercholesterolemia were randomly assigned to the bile acid sequestrant cholestryamine or to placebo. Treatment assignment was double blind. Both groups followed the same moderate cholesterol-lowering diet that provided about 400 mg of cholesterol per day and a polyunsaturated to saturate fat ratio of approximately 0.8. Average follow-up was 7.4 years. The participants in the trial were men age 35-59 years with a plasma cholesterol level of 265 mg/dl or greater and with an LDL level of 190 mg/dl or greater. Only men in good health and free of type III hyperlipoproteinemia and conditions associated with secondary hyperlipoproteinemia such as diabetes mellitus, hypothyroidism, nephrotic syndrome, hepatic disease, hyperuricemia and notable obesity were selected for the trial.

At the conclusion of the CPPT, average cholesterol levels in the cholestyramine group were reduced 13.4 percent, 8.5 percent greater than in the placebo group, and were associated with a statistically significant ($P>0.05$) 19 percent reduction in definite CHD death and/or definite nonfatal myocardial infarction. The degree of reduction of coronary risk was related to the amount of cholesterol lowering. CHD incidence in men who sustained a 25 percent fall in cholesterol was half that of men who remained at pretreatment levels. In general, CHD incidence fell 2 percent for every 1 percent fall in cholesterol. In addition, the incidence rates for new positive exercise electrocardiograms, angina, and coronary bypass surgery were also reduced.

Results of this clinical trial will be explored in the NIH Consensus Development Conference, "Lowering Blood Cholesterol to Prevent Heart Diseases," on December 12-14, 1984.

Investigators continue to examine the effects of specific dietary components on the incidence of cardiovascular disease and are particularly interested in the study of populations such as the Eskimos who consume large quantities of fish oils which contain long chain polyunsaturated fatty acids of the omega-3 series, that are quite different from the fatty acids found in animal or vegetable products. Based on data from the Eskimo population, these fatty acids are considered to have special effects upon plasma lipid and lipoprotein levels, cholesterol balance and platelet function. Also, in spite of large quantities of cholesterol contained in the Eskimo diet, the incidence of atherosclerotic vascular disease in these people appeared quite low, and death due to cardiovascular diseases such as myocardial infarction, aortic aneurysms and cerebrovascular accidents constituted only 1-2 percent of the total death rate. In contrast, Greenland Eskimos who have migrated to Denmark have acquired both Western diets and mortality rates.

Clinical studies are also being supported to investigate the effect of increased dietary potassium with and without sodium reduction on blood pressure, as well as the effects of weight reduction on hypertension. Four nutrition/hypertension clinical trials received support in FY 1983. Three of these dietary trials, sometimes referred to as "offspring" of the Hypertension, Detection, and Follow-up Program (HDFP), follow participants previously controlled by drugs in HDFP. These are the three-center Dietary Intervention Study of Hypertension (DISH) and a similar two-center trial, the Hypertension Control Program (HCP). A third trial, the Hypertension Prevention Trial (HPT), a four-center program, is testing the feasibility of preventing or reducing the usual rise in blood pressure with age in individuals with high normal blood pressure. A fourth and single-center Hypertension Intervention Trial (HIT) is studying individuals with mild hypertension.

Each of these four clinical trials uses similar dietary approaches but in different combinations of treatment to which participants are randomized. All use sodium restriction and weight control. Sodium restriction is combined with an increase in dietary potassium in DISH and HPT. Alcohol intake is also limited in HCP. The single-center HIT randomizes individuals to training in relaxation techniques and stress management, with or without dietary intervention.

One in every 20 persons in the United States is now affected by diabetes. New findings point to a diabetic population of over 11 million, with about 1 undiagnosed case of this disease for each of the Nation's 5.7 million known diabetics. In the past 6 years alone, over 3.6 million new cases of diabetes have been diagnosed--about 10 percent of them in children who now face a lifetime with the disease. Twenty-five percent of diabetics have heart disease, and diabetes is one of the four major risk factors for cardiovascular disease. Diabetes causes 20 percent of all cases of kidney failure, 15 percent of all blindness, and about 50 percent of amputations of the foot and and leg among adults.

The insulin-dependent form of diabetes mellitus (IDDM) is estimated to be approximately 10 percent of all known cases. One 2-year study, the Diabetes Control and Complications Trial, is under way to determine the feasibility of conducting a 7- to 10-year clinical trial to assess the relationship between metabolic control and the clinical course of early vascular complications in persons with IDDM. Blood glucose will be used as the primary indicator of metabolic control, and diabetic retinopathy will be the primary endpoint since it is a sensitive indicator of disease progression and may be affected by blood glucose control.

The feasibility study includes 252 patients between the ages of 13-39 years and having documented IDDM of 1-15 years duration, which are to be assigned randomly to either the standard or the experimental therapy group. Standard therapy consists of not more than two injections of insulin daily; an individualized meal plan providing for the total nutritional needs of the patient with reinforcement of the dietary program by the dietitian every 6 months; glucose tolerance

tests 3 to 4 times per day; an educational program; and a standard schedule of clinic visits and monitoring procedures every 3 months.

Individuals in the experimental treatment group receive intensive insulin therapy in one of two ways: by continuous subcutaneous infusion employing a pump (CSII) or as multiple daily injections (MDI) with at least three subcutaneous injections of insulin daily.

The same principles of dietary management are being followed in both the experimental and standard treatment group. The aim in the experimental group is to achieve and maintain glycemic control as near to normal as possible in the absence of significant hypoglycemia. The goal is to maintain the hemoglobin A1c level within 2 standard deviations of the mean for a sample of nondiabetic persons.

An integral part of the treatment regimen in both groups is an individualized meal plan that provides for the total nutrient needs of the patient, i.e., to promote normal growth and development in adolescents and maintain desirable body weight in the adults. The meal plan is quantitative in nature, identifying individual amounts of food and time of food consumption. It takes into account the patient's needs in terms of cost, food availability, beliefs, cultural influences, particular tastes and educational background. The initial dietary prescription is based on the American Diabetes Association's prudent fat diet and exchange lists; the dietitian will reinforce the dietary program. In patients with hypercholesterolemia, the prescribed cholesterol content will be less than 300 mg/day, with a polyunsaturated to saturated fat ratio of approximately 1.0 and no more than 10 percent of calories as saturated fat. The meal plan is made to be compatible with the rest of the therapeutic regimen, i.e., the insulin schedule and exercise patterns.

This 2-year randomized feasibility study attempts to determine: whether a clinically and statistically significant difference in the level of blood glucose control can be achieved between standard and experimental therapy groups as assessed by hemoglobin A1c and blood glucose measurements; the relative efficacy, utility, patient acceptability and safety of the experimental and standard therapy in the management of IDDM; and whether the biochemical and pathologic characteristics of IDDM can be measured and documented with acceptable precision and accuracy.

Studies to improve our understanding of the principles of nutritional therapy to control blood glucose levels for diabetics have recently received widespread attention. Since for years it has been believed that simple carbohydrates (sucrose, glucose, and fructose) are rapidly absorbed and cause a relatively large rise in blood sugar, whereas complex carbohydrates (or starches as found in rice, potatoes and wheat) are digested and absorbed slowly and thus result in smaller increases in blood sugar, diabetics were instructed to use complex carbohydrates in place of simple sugars. Recent data do not support the belief that dietary sugar (sucrose) aggravates high blood glucose in diabetics. These studies indicate that diabetics do not need to be denied sucrose as long as weight reduction is not neces-

sary and it is consumed in nutritionally balanced meals containing protein and fat. Including sucrose in the diabetic diet may increase overall compliance and thereby help to achieve the goals of diet therapy.

One study investigated the blood glucose response to the following different test carbohydrates: glucose, fructose, sucrose, potato and wheat starch in healthy subjects, and Type I (insulin dependent) and Type II (insulin independent) diabetics. The results indicate that meals containing sucrose do not produce significantly higher blood glucose levels than meals containing potato or wheat, whereas meals containing fructose result in the lowest blood glucose levels in all three subject groups. Thus, in both Type I and Type II diabetics, sucrose when consumed in a mixed meal with protein and fat did not produce a more rapid or a greater rise in blood glucose levels than did comparable amounts of potato or wheat starch. These data do not support the previously accepted dogma that dietary sucrose aggravates high blood glucose levels in diabetics. In addition, fructose, which can be incorporated into foods as a sweetener, appears to be preferable to sucrose in terms of blood glucose control.

The clinical expression of food allergy or food sensitivity is the result of a series of interactions between ingested food antigens, the digestive tract, tissue mast cells, circulating basophils and food antigen-specific IgE. Although the incidence of true food allergy in the general population is unknown, the incidence in children is estimated at 0.3 percent to 7.5 percent, decreasing with age. The incidence is higher in allergic children, approaching 25 percent of those with infantile eczema. Among adult atopic patients, 24 percent report allergic symptoms on eating or handling various foods.

The majority of allergic reactions to foods is believed to be IgE mediated, mast cell dependent immediate hypersensitivity or Type I reactions. Individuals have an inherited ability to form IgE on the mast cell surfaces in response to food-derived antigens causing immediate wheal and erythema reactions. Food antigen-specific IgE indirectly has been demonstrated to lead to the degranulation of mast cells in the gastrointestinal tract. The possible sequence of events after mast cell degranulation within the gastrointestinal tissues includes local changes in vasopermeability, stimulation of mucous production, increase in muscle contraction, stimulation of pain fibers, and recruitment of inflammatory cells. The clinical reflection of food allergy can be divided into that resulting from the action of offending foods on the initial contact organ, the digestive tract, and on secondary contact systems including skin, lungs, and blood vessels.

The diagnostic process in food allergy starts with a careful medical history and physical examination directed at distinguishing food hypersensitivity from other causes of adverse reactions to foods. The diagnostic tests for food hypersensitivity in common medical use relate to the diagnosis of food hypersensitivity or Type I reactions that occur within minutes to hours after exposure to specific foods. These tests are directed at an in vitro demonstration of IgE such as

in the radioallergosorbent test (RAST) and in the enzyme-linked immunosorbent assay (ELISA). The RAST is the most commonly used in vitro diagnostic test and has also proved useful as a research tool in the identification of the antigens in foods to which patients may react and in the standardization of allergenic extracts. The RAST, although used when skin testing with extracts might pose a hazard, is less sensitive than skin testing and more expensive. The ELISA, developed after RAST, also measures antigen-specific IgE and has the same potential as the RAST in the identification of food antigen-specific IgE.

Another in vitro test involves the examination of peripheral blood basophils from individuals with suspected food allergies in order to determine if they degranulate to dilute suspensions of food antigens. Degranulation requires the presence of IgE on the basophil-specific to the suspected food. Basophil degranulation testing correlates with skin tests but do not establish a diagnosis of food allergy.

In addition to in vitro tests for Type I hypersensitivity reactions, in vivo tests such as skin tests, elimination diets and food challenges are also used. Skin tests using water soluble extracts of foods are the most widely used diagnostic procedure in the evaluation of food hypersensitivity. The exposure of food antigen-specific IgE on the surface of the skin mast cells to specific food antigens leads to mast cell degranulation and a local wheal and flare reaction. This test, in general, is more sensitive than the in vitro tests.

Other in vivo tests examine the clinical consequences of the removal or addition of foods believed to lead to clinical reactions. The removal of foods is accomplished through the use of elimination diets. The elimination of a suspected food(s) from the diet should lead to an improvement in the patient's condition.

A food challenge may also be useful if the diagnosis of food allergy remains in doubt after a history, physical exam, laboratory and skin tests have been completed. Oral food challenges which may be given in an open, single-blind or double-blind manner are performed following the removal of suspected foods from the diet. The food being tested is administered as a test dose governed by the degree of suspected hypersensitivity. If no symptoms are reproduced by the test dose, the challenge should be repeated with the use of increasingly larger doses until the amount of food ingested exceeds that indicated in the dietary history. This procedure is repeated until all suspected foods have been examined.

In addition to immediate reactions to foods, examples exist of chronic gastrointestinal conditions associated with specific foods in certain individuals. These conditions include gluten-induced enteropathy, food-protein induced gastroenteropathy, and hypereosinophilic gastroenteritis. In such conditions, the immunologic mechanisms involved may include delayed hypersensitivity, antigen-antibody complex formation with complement activation, and IgE mediated mast cell degranulation. Since food-induced reactions are delayed in such diseases, elimination diets and food challenge procedures may be employed.

The research on food allergies to date implies that in no instance does any single diagnostic test make the diagnosis of food allergy. Rather, the results of these tests for food hypersensitivity are used to substantiate the clinical impression formed on the basis of the information obtained from the history, physical exam, and laboratory and skin tests.

Results of research on food allergy are interesting and multifaceted. One study is investigating the role of food hypersensitivity in atopic dermatitis, particularly the role of IgE mediated reactions to food. The 31 children included in this study, who were allergic to a variety of foods and received food challenges, experienced many allergic reactions in various organs. These organs are listed in decreasing order of frequency: skin alone; skin and gastrointestinal tract (GI); skin and nose; skin, GI, nose and lungs; GI alone; and nose alone. Preliminary data suggest that children lose their hypersensitivity if they remain on a restricted diet for a finite time period. It is not known whether they lose their hypersensitivity without diet restriction. In addition, breast-fed infants allergic to foods experienced allergic reactions when they were nursed after their mothers consumed the particular food to which they were allergic.

This study showed a negative allergic skin test to be an excellent means of excluding immediate hypersensitivity to foods in children with allergic skin rashes. Positive tests, however, were merely useful guides to determine which foods needed to be studied by a more definitive test, i.e., a double-blind oral food challenge. In children with food allergies, the mast cells released histamine and serum histamine levels rose after an oral challenge with food. In non-allergic children, serum histamine levels did not rise in response to food.

Research will continue to make attempts to define the fraction of a particular food that causes the allergic response. Results of this research will enable us to better understand antigen penetration of the gastrointestinal tract as well as possible ways to alter the antigen so that it is less likely to enter the systemic circulation. Using specific food antigens will improve the diagnostic tests used to randomize and treat allergic individuals suffering from allergies.

Studies on the role of nutrition in central nervous system disorders have been under way for many years. Since 1956, investigators have carried out studies in Guam to examine the unusually high incidence of amyothrophic lateral sclerosis (ALS) and parkinsonism-dementia (PD), both of which occur frequently in the same Guamanian Chamorro families and occassionally in the same individual. ALS affects the motor neurons of the brain and spinal cord, resulting in progressive weakness, atrophy, and eventual paralysis and death while PD results in slowness of motor activity, disturbances in gait, rigidity, tremor and severe dementia. A high incidence of both ALS and PD has also been documented in two additional western Pacific populations: the

Japanese living in the Kii Peninsula of Honshu island and the Auyu and Jakai living in villages of the southern coastal plain of West New Guinea.

In all of these populations, severe deficiencies of calcium and magnesium have been noted, while high concentrations of aluminum have been found in drinking water and garden soil. Subtle disturbances in calcium and vitamin D metabolism have been noted in ALS and PD patients, while cortical bone loss has been found in many children and adults in Guam.

Prominent concentrations of calcium and aluminum in brain tissue from Guamanian Chamorro patients with PD have been imaged for the first time by NIH scientists. Using computer controlled electron beam x-ray microanalysis, the scientists found the distribution and produced images of calcium and aluminium in neurofibrillary tangle (NFT) bearing neurons within the hippocampal region of the brain. The elemental images show the striking localization of both calcium and aluminium within the cell body and axonal process of the same NFT-bearing hippocampal neurons in this dementing disease. Deposits of calcium and aluminum were not found in non-NFT bearing neurons in the hippocampus of the patients or controls.

These findings support the hypothesis that defects in the mineral metabolism and secondary hyperparathyroidism provoked by chemical deficiencies of calcium and magnesium have led to an increased absorption of toxic metals and deposits of calcium and alumininum in the central nervous system of these patients.

In research on the role of diet in the development of dental caries, a variety of common snack foods are being tested for cariogenicity. In this research, rats are fed their essential nutrition by intubation and receive test food snacks by mouth by way of a feeding machine in order that in a reproducible way, only the test food comes into contact with the rat's mouth. Prior to the feeding experiment, rats are inoculated with Streptococcus mutans. After 5 weeks on the feeding machine, the rats' mouths are scored for dental caries. These researchers have found peanuts and corn chips to be uniformly low in cariogenicity. Other tested food items, listed in order of increasing cariogenicity, included: saltines and granola; potato chips, pretzels, graham crackers, raw starch and milk chocolate; bread; cake doughnuts, french fries and sucrose; with cupcakes demonstating significantly more cariogenicity than sucrose.

Nutritional support services are an extremely critical component of appropriate medical care for patients suffering from cancer, burns, trauma, infection, gastrointestinal diseases, and liver, renal, cardiovascular and pulmonary diseases, as well as for elderly patients, infants with severe gastrointestinal congenital anomalies, and low birth weight infants. The ability to provide adequate nutrition to individuals who cannot properly ingest, digest, or absorb food has been a major technological achievement over the past 15 years. Nutritional support of patients provided either parenterally or enterally is essential in order to permit normal growth, develop-

ment, and maintenance of health. Apart from its obvious therapeutic importance, research on total parenteral and enteral nutrition allows investigators to probe and manipulate metabolism and physiology.

The pioneering work in parenteral and enteral nutrition research began in the mid 1940's with some of the earliest research involving the problem of nitrogen balance for patients with surgery. In the late 1960's significant advances were made in TPN provided to the neonate. Current research has used these early studies as a foundation for pursuing further advancements in the field not only as they pertain to the nutrient support of the newborn infant, but also to the elderly and patients with special nutrient needs.

The NIH has actively encouraged continued research in this important area for many years. In 1979, the NIH-NCC sponsored a 2-day workshop entitled "Nutritional Support of the Patient: Research Directions for the 1980's," in order to develop research priorities (or directions) for studying the effects of parenteral and enteral nutritional support of sick patients. It was recognized that TPN is an effective lifesaving procedure for patients with selected conditions, however, it does not cure infection, cancer, pulmonary insufficiency, regional enteritis, cirrhosis or a wide variety of other ills. For approximately 80 percent of hospitalized patients, nutrition is simply a means to maintain body mass and function until other treatment modalities are given the opportunity to affect the disease. The workshop focused attention on the research needed to delineate the proper uses of this powerful new technology.

In 1982, a joint PA, "Studies on the Nutritional Support of the Patient" was issued jointly by NHLBI, NIA, NIADDK, NICHD, and NIGMS which called for investigations on the impact of nutritional status on immune defense functions in lung development during fetal life and in patients with chronic pulmonary disease; on the assessment of the efficacy of current enteral and parenteral therapies for the elderly and the development of optimum methods for meeting the nutritional requirements of elderly patients, particularly those with multiple disorders and under medication; the interaction of nutrition, infection and immunity and the effects of infectious agents on nutrient metabolism in patients and in animal models; nutritional support of the patient as it affects the nutritional status of the whole individual, such as with obesity, chronic renal failure (end-stage renal disease), anorexia nervosa and surgical trauma; the effect of disease stress and related conditions on nutritional requirements and the effect of nutrient intake levels on the course of specific diseases. Research applications in response to this PA have expanded our knowledge about the appropriate nutritional support services necessary to sustain life, as well as to improve the quality of life.

One specific area of research interest is the metabolic effects induced by long-term TPN. Scientists attempt to determine the safe range of levels and proportions of all nutrients and other substances required for the normal functioning of cells and the maintenance of well-being in patients that depend on long-term TPN for health maintenance and survival. However, more research is needed to study

differences in metabolism, changes in organ and endocrine function and nutritional requirements (safer ranges and proportion of essential nutritional factors) in patients who are dependent on TPN for long-term sustenance.

Different aspects of research on TPN are being carried out by investigators from five of the Clinical Nutrition Research Units where studies are under way on the development of fatty livers in patients treated with parenteral hyperalimentation and the occurrence of hypoglycemia following the discontinuation of parenteral hyperalimentation; on the optimal intake of zinc and copper in pediatric patients requiring TPN or defined formula diets; preliminary assessment of the efficacy of supplemental enteral tube feedings as an adjunct to combination chemotherapy in patients with small cell and anaplastic carcinoma of the lung; and nutritional assessments as predictors for determining the need for special nutritional support in presurgical patients. Efforts are being made at the CNRU's for expanding the nutritional support services offered to the patients.

TPN treatment for severe malnutrition resulting from gastrointestinal diseases has been often associated with the appearance of a disabling bone disease, characterized by normal or elevated serum calcium and phosphorous, normal or reduced serum PTH, substantial hypercalciuria, and reduced serum levels of $1,25(OH)_2D$ with normal levels of other vitamin D metabolites. Studies are making attempts to identify the course of the development of the biochemical abnormalities of Ca, P, vitamin D metabolites and PTH as TPN is initiated, to evaluate specific components in the TPN solutions that may be pathogenic, and to evaluate the various therapeutic manuevers including parenteral $1,25(OH)_2D_3$.

Studies on intestinal adaptation have shown that nutrients in the lumen and metabolic balance are the principal stimuli for changes in intestinal absorption and mass. Investigations are under way to examine the effects of these nutrients and metabolic balance in fasted rats compared to rats nourished by parenteral or enteral nutrition on intestinal function. The long-term objective of such studies is to allow for better nutritional support of the patients requiring parenteral or enteral nutrition due to inflammatory bowel disease and the short bowel syndrome.

Patients with chronic renal failure also require TPN, therefore, developing the optimal dietary regimen for such patients is essential. Studies are examining various compositions of amino acids and N-free analogs in terms of their effects on short-term and long-term nitrogen balance in these patients. In addition, it has been shown that continuous nasogastric alimentation with a mixture containing the amino acids plus oligosaccharides has resulted in improved protein nutrition and highly efficient energy conservation. Research continues in this area examining infusion schedules that are primarily nocturnal vs. continuous and that replace ornithine with alanine. Another study is attempting to develop a practical technique for quantitating the degree to which individual branched chain ketoacids become incorporated (after transamination) into protein.

The nutritional support of cancer patients is an important area of research which tests the hypothesis that the administration of TPN is more effective than normal hospital regimens in maintaining adequate nutritional status and that it does not adverseely affect tumor control. Both clinical studies and animal studies attempt to assess the effectiveness of TPN in maintaining the immune response and thereby lessening or moderating the complications associated with cancer treatment.

Studies have shown that the nutritional needs of the growing tumor take priority over the nutritional needs of the host as measured by a decreased cell proliferation activity in some of the host tissues and by the wasting of the carcass mass. Research investigations are trying to determine how the metabolism of the host might change in the face of the increasing demands for glucose by the growing tumor by giving rats with and without tumors total parenteral feedings of defined diets where only the levels of glucose are varied.

Other studies are evaluating the effects of preoperative intravenous hyperalimentation (IVH) on tumor growth parameters as measured by cell kinetics in patients with rectal cancer. Tumor tissue and adjacent normal rectal mucosa will be analyzed for growth fraction, percent cells in S-phase and DNA, RNA, and protein content as measured by flow cytometry. Additional studies examine the manner in which hepatomas utilize pyridoxal phosphate since some investigators have shown that Morris hepatomas differ significantly from liver in their ability to convert precursor B_6 vitamin forms such as pyridoxine to coenzymatically active pyridoxal phosphate. One study is investigating the effect of parenteral nutrition on protein and fat metabolism and the effectiveness of utilizing ^{15}N as a tracer to measure protein synthesis rates in two groups of adult cancer patients with operable tumors.

Since available milk-based formulas are unable to satisfy the needs of the very low birth weight neonate, total parenteral nutrition has been relied on heavily to provide adequate nutrition. Studies of low birth weight infants and the evidence of sufficient protein from feeding either human milk or artificial formulas that differ in protein and energy content examine the metabolism of intravenously administered amino acids in an effort to design a mixture of amino acids that results in a completely normal plasma amino acid pattern. Such research provides the data needed for the overall improvement of the nutritional management of low birth weight babies. Other studies examine aberrant maternal and fetal metabolic systems, such as the diabetic mother, fetus and neonate; the intrauterine growth retarded fetus and neonate; and the premature infant, and the effects of nutrition intervention to neonatal outcome.

In the premature infant, the precise interrelationships of essential exogenously derived hematologic nutrients, i.e., tocopheral, selenium, iron, folate and vitamin B_{12} are not well-defined. Studies are examining the interaction and requirements of these nutrients in terms of optimal hematopoietic development. The levels of transport

proteins, as well as maternal nutritional, serological and hematopoietic data, will be studied.

The recent introduction of fat emulsions for intravenous use has given the neonatologist a tool to provide sufficient calories parenterally while limiting glucose and amino acids to amounts that are well tolerated. Research is under way to investigate the optimal means of administration of fat emulsions, i.e., that produces the least changes in the patterns of plasma lipid values. These studies will clarify if infusions of fat emulsions cause harmful effects on levels of free bilirubin in plasma and on diffusion of oxygen in the lungs and on levels of plasma lipids.

Nutrition research on the effects of food-borne contaminants and additives on the biological systems encompasses studies of chemicals, metals and natural products such as aflatoxin. Investigations consider how these contaminants or additives, alone or in mixtures, alter absorption, metabolic and excretory functions of the gastrointestinal tract. One study revealed that the rainbow trout is more sensitive than the Coho salmon to aflatoxin B_1 as a hepatocarcinogen. Initial DNA damage in the salmon was shown to be less than that observed in the trout.

Research has shown that the major fraction of the human body burden of heavy metals is derived from the diet under normal conditions. One study is investigating the factors that control absorption of toxic metal contaminants from the diet. Data indicate that a saturable membrane mechanism exists for the absorption of the heavy metal, cadmium, from the rat jejunum. Testing the hypothesis that cadmium uptake results from the interaction of the metal with mechanisms essential for the absorption of calcium or zinc led to the finding that the interaction from the intestine is not competitive in nature. Cadmium does not compete with other metals for common transport sites. Certain bile salts have been identified as inhibitors of cadmium movement, while milk has been shown to stimulate the absorption of cadmium into the body cells. This finding may explain why neonatal organisms are at special risk of metal intoxication. Investigations done with rats on the effects of lead on absorptive functions of the gastrointestinal tract have shown that the levels of lead that cause significant hematological and renal toxicity does not alter the gastrointestinal transit time of lead. When compared to pair-fed animals, the animals fed lead did not have a significant change in the percentage of water content of the feces. The significant increase in the total 24-hour fecal weight in these animals was most likely due to unabsorbed lead. In ad lib fed animals, however, lead produced a significant decrease in food consumption and a corresponding decrease in total 24-hour fecal weight. Thus, lead intoxication achieved in these experiments produced constipation primarily through its anorexic effect and not by a direct effect on mucosal or smooth muscle cells of the gastrointestinal tract.

Other studies have focused on the effects in animals of 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) and related compounds on loss of body weight, hyperlipidemia and hypoglycemia. Data from such studies

indicate that compared to guinea pigs treated with TCDD and fed ad lib the guinea pigs treated with TCDD and given total parenteral nutrition support do not lose weight or become hyperlipidemic. These animals do however experience lethargy, increased mucus-like secretions, and altered serum parameters suggestive of compromised hepatic function. The hyperlipidemia in treated guinea pigs fed ad libitum may be a secondary effect of weight loss and adipose tissue mobilization.

Previous work suggests that the effect of TCDD on body weight loss may be mediated by the hypothalamus and that hypothalamic function may be altered by secretions from the thymus. In all animals between 2 and 70 days of age, the thymus appeared to have a relatively constant high level of receptors for TCDD. Additional studies will attempt to determine the direct effect of TCDD on hypothalamic function as well as its effect on various parameters related to lipid and carbohydrate metabolism in rats and guinea pigs. Preliminary data suggest that lipid oxidation in rats may be significantly altered by TCDD.

II.

NUTRITION COORDINATING COMMITTEE

Nutrition is an important, crosscutting program area within the NIH. For this reason, the nutrition program is coordinated through the Nutrition Coordinating Committee that operates out of the Office of the Director and is advisory to the Director. The Committee is the focus for the review and coordination of nutrition research and research training priorities, and is responsible for the development of the NIH program in biomedical and behavioral nutrition research and research training. This focus minimizes duplication of effort among the Institutes and identifies areas where research, research training, and manpower development in nutrition need to be advanced.

COMMITTEE STRUCTURE

The Nutrition Coordinating Committee operates out of the Office of the Director and is advisory to the Director, NIH. The membership of the NCC consists of representatives from the 11 Institutes and the Division that support nutrition research. Additional NIH offices and other agencies of the Department of Health and Human Services have liaison representatives to the committee. As of September 30, 1983, the NCC was composed of the Chairman, 21 members and alternates, 1 consultant, 10 liaison representatives and alternates from interested offices within the NIH, and 6 liaison representatives and alternates from other agencies within DHHS. The mandate of NCC appears in appendix A.

The committee, established in 1975, reviews and comments on the plans, execution, and results of pertinent Bureau, Institute, and Division research efforts relating to nutrition in order to develop the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training. In addition to staffing the NCC, the office staff provides information requested by the Office of the Director, and represents NIH in numerous activities involving nutrition research at DHHS, other Federal and non-Federal agencies, industry, and professional societies. The NCC office also maintains information on national and international nutrition meetings and conferences.

NCC meetings are normally held once a month and are attended by the members, liaison representatives, and committee office staff. In addition to the regular business of the committee, special presentations on subjects of current interest to the NCC are frequently made by scientists from other agencies or groups. The NCC meetings are followed by scientific seminars in nutrition in order to highlight research in nutrition, especially that research carried out by intramural scientists at the NIH, and to keep the NCC representatives informed of research developments in nutrition.

In addition to committee activities, a number of special activities were carried out through the NCC Subcommittee on Nutrition Education. In FY 1983, the Subcommittee on Nutrition Education consisted of representatives from NCI, NEI, NHLBI, DRR, DRS, the Clinical Center, the Office of Communications and the NCC office.

COMMITTEE ACTIVITIES AND ACCOMPLISHMENTS

Scientific Seminars

In FY 1983, eight scientific seminars in nutrition were presented by extramural and intramural scientists engaged in nutrition research at NIH as well as scientists involved in nutrition research at other government agencies. Descriptions of the seminars follow.

1) "Obesity as an Independent Risk Factor for Cardiovascular Disease," was presented by Helen B. Hubert, Ph.D., Epidemiology and Biometry Program, NHLBI, at the November 4, 1982, NCC meeting. A summary of her presentation is given below.

Many studies have shown that the incidence of certain types of cardiovascular disease (CVD), particularly coronary heart disease and stroke, is greater in heavier persons. Up to now, the consensus has been that the increased risk among heavier persons is due primarily to the influence of the associated risk factor profile and not to the degree of obesity per se. This study reexamined the relationship between the degree of obesity and the incidence of cardiovascular disease in 2,252 men and 2,818 women, ages 28-62 years, of the original Framingham cohort. The subjects were free of clinically recognizable CVD at the first study examination that took place between 1949 and 1950; manifestations of CVD included coronary heart disease, congestive heart failure, stroke and intermittent claudication. They were classified at initial exam by Metropolitan Relative Weight (MRW) or percentage of desirable weight (ratio of actual weight to desirable weight x 100) and observed for 26 years for the development of CVD. Desirable weight was derived from the 1959 Metropolitan Life Insurance Company tables by taking the midpoint of the weight range for the medium build at a specified height.

During the 26-year followup, 870 men and 688 women developed CVD, with coronary heart disease accounting for a large proportion of the events (75 percent in men and 66 percent in women). The risk of CVD increased in both men and women with increasing MRW at the time of entry to the study; the association of weight to CVD incidence was most pronounced in those younger than 50 years. The incidence of coronary disease, the most frequent manifestation of CVD, increased with increasing MRW and the gradient of risk was steeper in the younger men and women.

Multiple logistic regression analyses showed that MRW predicted the 26-year incidence of coronary disease (both angina and coronary disease other than angina), coronary death, and congestive heart failure in men independent of age, serum cholesterol, systolic blood pressure, cigarettes/day, left ventricular hypertrophy, and glucose intolerance. MRW in women was also positively and independently associated with coronary disease, stroke, congestive heart failure and coronary CVD death. The strength of the association was greatest for MRW and sudden death in men, and congestive heart failure in women. The relationship between MRW and coronary heart disease was stronger in males than in females because of the greater influence of this characteristic on the development of angina in men.

MRW ranked only behind age and blood pressure as a predictor of total CVD in women, while in men it ranked behind all other risk factors. The 26-year incidence of intermittent claudication, indicative of peripheral vascular disease, however, did not appear to be clearly related to the degree of overweight in either men or women.

The relationship of weight change to CVD incidence was examined by comparing the self-reported weight at age 25 with the weights at initial Framingham examination. Change in MRW was positively and significantly related to risk of CVD over the 26 years in both sexes, even after adjustments for the effects of MRW at age 25, age at exam 1, and risk factor levels. The data showed that weight gain after the young adult years conveyed an increased risk of CVD in both sexes that could not be attributed either to the initial weight or the levels of the risk factors that may have resulted from the weight gain.

The degree of obesity in Framingham men and women was an important long-term predictor of CVD incidence, particularly among the younger members of the cohort. Moreover, obesity in both sexes did not exert its influence solely through its association with the coexisting risk factors. Obesity predisposed individuals to premature CVD. Differences observed in the sexes could have been due to the fact that MRW represented a somewhat different measure of body mass in each sex, since excess weight resulted from muscularity more often in males than females. For example, although MRW was not an independent predictor of myocardial infarction in men, subscapular skinfold measurements were significantly and independently associated with this outcome.

In addition to the relationship observed between MRW and disease risk, the change in MRW after the young adult years also made an independent contribution to the prediction of CVD. At any level of MRW at age 25 years, weight change was positively and significantly associated with CVD risk in both sexes with a stronger relationship observed in men. These results illustrate not only the detrimental effects of weight gain, but also the benefits of weight reduction in obesity. The study also suggests that men may be more generally sensitive than women to the effects of weight change, because its impact on disease could not be attributed solely to the resulting levels of the risk factors.

Although MRW at entry to Framingham was a better predictor of CVD incidence than MRW at age 25, analysis of the data indicate that the risk of CVD was most pronounced among those subjects who stayed in the heaviest weight class between exam 1 and age 25 years. Thus, the duration of obesity on incidence of CVD is an important consideration.

Some effects of overweight may be evident only after followup over long periods of time. Both the Framingham and Manitoba studies found obesity to be an independent predictor of disease on long-term observation only; at the 8-year followup in Framingham men a significant association between MRW and coronary disease incidence was observed, while in women a significant association was observed at 14 years.

Dr. Hubert concluded that leanness and the avoidance of weight gain before middle age are advisable goals in the prevention of CVD for most American men and women. In addition, intervention on the well-established risk factors for disease should be accompanied by weight loss in the overweight individual.

2) "Nutritional Aspects of Mineral Metabolism" was presented by Charles Pak, M.D., Director of the Clinical Research Center, University of Texas Health Science Center at the January 6, 1983, NCC Meeting. A summary of his presentation is given below:

Disturbances in mineral metabolism can result from an abnormal dietary intake of sodium, calcium, purines, oxalates, carbohydrates and proteins. A number of balance studies have shown that calcium absorption is increased by a low calcium diet and decreased by a high calcium diet. It appears that the increase in calcium absorption is due to an increased synthesis of 1,25-dihydroxy vitamin D. The regulatory mechanism involves a small diminution in serum ionized calcium concentration which stimulates parathyroid (PTH) secretion, which in turn enhances the conversion of 25 hydroxycalciferol to 1,25-dihydroxy vitamin D by the kidney. This potent vitamin D metabolite then stimulates intestinal calcium absorption in order to restore serum calcium to normal. This hypothesis is supported by the finding of significantly higher values for serum PTH and 1,25-dihydroxy vitamin D after 4 weeks on a low calcium diet as compared to values after 4 weeks on a high calcium diet.

A study to determine whether calcium absorption in the ileum or the jejunum is more sensitive to changes in dietary calcium intake has shown that after 4 weeks on a low calcium diet jejunal and ileal calcium absorption rates were approximately equal, and that a change from a low to a high calcium diet did not significantly alter calcium absorption in the jejunum, but decreased ileal calcium absorption by 45 percent. After 8 weeks on a high versus a low calcium diet, jejunal calcium absorption was significantly less. The difference in jejunal absorption rates after these two dietary periods was 43 percent, while the difference in ileal calcium absorption was 89 percent. These results suggest that the ileum is more sensitive than the jejunum to variations in dietary calcium intake with respect to calcium absorption.

In addition, these studies revealed that the low calcium diet enhances magnesium absorption in both the jejunum and the ileum, although only the changes in the ileum were statistically significant. The loss of adaptation in the intestine leads to diseases of mineral metabolism with underadaptation characterizing postmenopausal osteoporosis and overadaptation typical of absorptive hypercalciuria.

Other studies have shown that an oral sodium (Na) load may induce hypercalciuria in previously normocalciuric subjects and may also increase intestinal calcium absorption. The hypothesis is that an oral sodium load leads to hypercalciuria (renal leak of calcium), which leads to secondary hyperparathyroidism and a subsequent increase in 1,25-dihydroxy vitamin D synthesis creating an increase in intestinal calcium absorption. For example, normal subjects in one study showed significant increases in serum 1,25-dihydroxy vitamin D and intestinal calcium absorption in response to a 10-day sodium load. They also appeared to have a small increase in serum i parathyroid hormone.

This hypothesis that stimulation of parathyroid secretion and 1,25-dihydroxy vitamin D synthesis is a critical factor for the adaptation of intestinal calcium absorption to salt loading was further reinforced by data from patients with postsurgical hypoparathyroidism. These patients had low serum i PTH and urinary cylic AMP levels which did not change with salt loading, and there was no change in serum 1,25-dihydroxy vitamin D or fractional intestinal calcium absorption in response to salt-induced calciuresis. The potential for serum calcium reduction in patients with hypoparathyroidism indulging in excessive salt intake may be relevant to the management of these patients. The patients with hypoparathyroidism, upon treatment with ergocalciferol, had normal levels of serum 1,25-dihydroxy vitamin D which then restored calcium levels to normal and permitted adequate urinary calcium measurements during the dietary sodium manipulations.

Dietary sodium therefore may be relevant in the pathogenesis of postmenopausal osteoporosis and nephrolithiasis. The induced hypercalciuria from the sodium load causes a compensatory rise in intestinal calcium absorption. This compensatory mechanism may be lacking in postmenopausal osteoporosis. The inability of the intestine to adapt to increased renal calcium losses may contribute to the bone disease. In addition, a high sodium intake may exaggerate calcium stone disease since the sodium urate-induced crystallization of calcium oxalate may be promoted.

Other studies of mineral metabolism consider the absorption of oxalate from food and the impact of oxalate loads on urinary calcium excretion. In calcium nephrolithiasis with increased calcium absorption (e.g., absorptive hypercalciuria), urinary oxalate may be moderately high because of increased oxalate availability from reduced calcium oxalate complexation in the intestinal tract. Thus, the avoidance of oxalate rich foods often has been recommended in the management of oxalate nephrolithiasis.

The absorption of oxalate from food is a function of the oxalate content and bioavailability in specific food items, as well as the efficiency of oxalate absorption. Analysis of foods has revealed that the oxalate content is high in spinach (1,236 mg), moderate in chocolate (126 mg) and tea (66 mg), and low for vegetable juice, cranberry juice, pecans and orange juice (2 to 26 mg). The urinary oxalate increased by 29.3 mg during 8 hours after ingestion of spinach, however, it rose by less than 4.2 mg from consumption of other food items. The bioavailable oxalate (percent of total appearing in urine) was much less from food items of high or moderate oxalate content (spinach and chocolate) than from standard solutions of sodium oxalate (2.6 versus 6.5 to 7.3 percent). Thus, among the food items tested, only spinach was capable of causing hyperoxaluria in normal subjects. In patients with ileal disease, oxalate absorption is high because of greater bioavailability and increased mucosal permeability.

Other causes of renal hypercalciuria are the ingestion of metabolizable carbohydrates and a high protein intake from animal sources

which may provoke a negative calcium balance and potentially cause bone disease. This high protein intake may also be a risk factor for stones, since it increases the renal excretion of calcium, oxalate, and uric acid and reduces the excretion of citrate.

3) "Anorectic Properties of Amphetamines: Sites of Brain Action," was presented by Steven M. Paul, M.D., Chief, Clinical Neuroscience Branch, NIMH, at the February 3, 1983, NCC meeting. A summary of his presentation is given below.

It is known that amphetamines and related phenylethylamine derivatives have psychostimulant, hyperthermic, vasoconstrictor, and anorexic properties. In order to delineate the membrane (neuronal) sites of action, the membrane binding of (+)-[3H]amphetamine was examined in rat brain. Saturable and stereospecific binding sites for (+)-[3H]amphetamine are reported to be located mainly in the synaptosomal membranes, sensitive to heat and proteolytic enzymes, and regionally distributed within the central nervous system. The density of these binding sites varies among brain regions and is highest in the hypothalamus and brainstem.

Data indicate that these sites may be pharmacologic receptors mediating the anorexic action of these compounds. A biphasic saturation curve was consistently observed suggesting the presence of multiple binding sites; scatchard analysis of the data reveals two specific binding sites with apparent affinity constants (Kd values) of 96 nM and 270 nM. The values of maximum binding (Bmax) corresponding to these two sites were 95 and 215 femtomoles per milligram of protein. The presence of two binding sites was also apparent with the displacement of specific (+)-[3H]amphetamine binding by various amphetamine like drugs (i.e., phendimetrazine, aminoxaphen, methamphetamine and diethylpropion).

In order to ascertain whether (+)-[3H]amphetamine binding is associated with any of the known neurotransmitter or drug receptors, a series of phenylethylamine derivatives as well as chemically unrelated receptor agonists and antagonists were examined for their potency in competing for specific (+)-[3H]amphetamine binding. This binding appears not to be associated with any neurotransmitter or drug receptors such as alpha- or beta-adrenergic, cholinergic, dopaminergic, opiate, serotonergic, or benzodiazepine receptors. In contrast, several amphetamine derivatives including p-chloroamphetamine, fenfluramine, aminoxaphen, and methamphetamine were more potent than amphetamine in displacing (+)-[3H]amphetamine binding. Furthermore, the relative affinities of a series of phenylethylamine derivatives for (+)-[3H]amphetamine binding sites in hypothalamic membranes is highly correlated to their potencies as anorexic agents ($r = 0.97$, $P < 0.01$).

Dr. Paul concluded that these results demonstrate that saturable and specific binding sites for (+)-[3H]amphetamine exist in rat brain localized in the neuron. These sites appear to be specific for amphetamine and related phenylethylamine derivatives. The high correlations observed between the potencies of a series of ampheta-

mine-like drugs in displacing specific (+)-[3H]amphetamine binding in vitro and in producing anorexia in rats suggest that these sites may represent receptors mediating the anorexic actions of amphetamines and related drugs. More research is needed to determine whether the sites are located in presynaptic or postsynaptic membranes in order to clarify if the sites modulate release, reuptake, or response of other neurotransmitters involved in the regulation of appetite.

4) "The Salty Side of Hypertension" was presented by Mordecai Blaustein, M.D., Chairman and Professor, Department of Physiology, University of Maryland School of Medicine at the March 3, 1983, NCC Meeting. A summary of his presentation is given below.

The etiology of essential hypertension, a disease prevalent in cultured societies, is unknown. Since abnormal sodium metabolism appears to play a critical role, one hypothesis being tested is that an increase in the circulating concentration of an inhibitor of (Na+ and K+) ATPase is responsible for the increased peripheral vascular resistance in essential hypertension.

The kinetic behavior of (Na+ and K+) ATPase was studied in the presence of a saline solution (control) and deproteinized plasma samples derived from one normotensive individual, and from a patient with essential hypertension. In each case, about 1.5 minutes were required to reach a steady state of enzyme activity, which then lasted for at least 10 minutes. The normotensive plasma produced no inhibition of activity compared to the control, while the hypertensive sample produced a 14 percent inhibition of steady-state activity that remained constant for the next 10 minutes of the reaction. This result demonstrates the presence of an increased level of an inhibitor of (Na+ and K+) ATPase in hypertensive plasma that has a rapid onset of action.

Bioassays and cytochemical assays of plasma and urine have been used to assess the presence of a Na+ pump inhibitor. After assaying plasma samples from 20 normotensive individuals and 26 patients with essential hypertension, a significant correlation was found between mean arterial blood pressure [MAP] and (Na+ and K+) ATPase inhibition when the hypertensive group alone was analyzed ($r = 0.46$, $P < 0.01$). No significant correlation was found for the normotensive group. A greater correlation coefficient and significance values were observed between MAP and (Na+ and K+) ATPase inhibition when the normotensive group was included in the overall analysis [$r = 0.73$, $P < 0.0005$]. The correlation was similar [$r = 0.77$, $P < 0.0005$] when diastolic pressure (instead of MAP) was used.

Data were also collected on red cell Na+ levels, digoxin-like immunoreactivity in plasma samples, MAP, and percentage (Na+ and K+) ATPase inhibition. The mean essential hypertensive MAP was more than two standard deviations above the mean normotensive MAP. Mean percentage inhibition of (Na+ and K+) ATPase was significantly elevated in the essential hypertension group, as was the intracellular erythrocyte Na+ content. Analysis of the plasma samples failed to demonstrate a significant elevation of digoxin-like immunoreactivity in the plasma samples that inhibited the (Na+ and K+) ATPase.

Data have also shown that inhibition of Na+ pumps in vascular tissue by ouabain results in increased resting tone and enhanced reactivity to catecholamines. This inhibition may lead to a net accumulation or redistribution of intracellular Ca++ as a consequence of a Na+-Ca++ exchange mechanism at the vascular smooth muscle cell plasma membrane. The increase in intracellular Na+ by Na+ pump inhibition leads to a net uptake of Ca++ and thus, to an increase in peripheral vascular resistance--the hallmark of the hypertensive process. Inhibition of Na+ pumps in sympathetic nerve terminals may enhance catecholamine release and reduce reuptake and thus contribute to the maintenance of elevated vascular smooth muscle tone.

Dr. Blaustein concluded that elevated levels of (Na+ and K+) ATPase inhibitor in the plasma may be the result of a congenital or acquired defect in the renal natriuretic capability in individuals prone to hypertension. Excessive Na+ ingestion by these individuals would result in Na+ and water retention and the tendency towards expansion of extracellular fluid volume unless compensatory physiological mechanisms are brought into play. These data suggest that one compensatory mechanism may be an increased secretion of an inhibitor of (Na+ and K+)ATPase that enhances Na+ excretion. These observations imply that, even in normal circumstances, the activity of the Na+ pump may be directly modulated in vivo by humoral substances.

5) "Nutrition Education in Medical Schools: If I Had My Way" was presented by Maurice E. Shils, M.D., Sc.D., Professor of Medicine, Cornell University Medical College, and Director of Clinical Nutrition, Memorial Sloan-Kettering Cancer Center, New York, at the May 5, 1983, NCC meeting. A summary of his presentation is given below.

A multidisciplinary effort to assist and encourage education in clinical nutrition has led to the establishment of a Regional Center for Education in Clinical Nutrition in the New York-New Jersey Metropolitan Area. This center, which began in 1981, serves as a nutrition resource, planning and evaluation agency for faculty in 10 medical schools, 5 dental schools, 2 schools of osteopathy, and major teaching hospitals in the region.

The activities of the center include: liaison and consultation activities with faculty in the schools and the development of model curriculum and clinical teaching objectives in nutrition; periodic evaluation of curriculum; the organization and support for expert nutrition consultants; compilation of existing clinical nutrition electives and the stimulation of cooperative efforts; compilation of a regional resource directory; and convening periodic regional conferences to discuss and stimulate efforts at improved teaching in nutrition.

The effectiveness of the center depends upon the interest and voluntary cooperation by the faculty in the various schools. Since its initiation a number of interesting observations on the availability of nutrition courses and commitment of the faculty to nutrition at

the various schools. For example, in terms of nutrition in the curriculum it appears that required or elective courses in nutrition are available in most schools with almost all in the first or second years, and that formal clinical electives in nutrition are specialized and therefore involve few students. Little, if any, effort is made to analyze or evaluate the influence of a particular nutrition course at the time of its completion or during the student's clinical years. None of the schools have a progressive 4-year curriculum in nutrition. A major obstacle is the failure to develop interdepartmental planning, evaluation and teaching efforts in clinical nutrition. Clinical nutrition faculty members operate in relative isolation as reflected in a lack of interdepartmental teaching contacts; the regional curriculum committees do not have any subcommittee on nutrition, nor are there any coordinators of nutrition curriculum. Appointments to the faculty of a school are rarely made on the basis of the school's commitment to nutrition, and a faculty member interested in nutrition usually has a major responsibility in another area that requires a major time commitment.

Dr. Shils concluded that efforts such as those of the Regional Center for Education in Clinical Nutrition, directed to improve curriculum development in nutrition in medical schools, dental schools, etc. must be targeted to each individual school on a continuous basis, with both short-term and long-term goals, as well as with an administrative effort to keep alive the efforts of progress.

6. Different aspects of the topic "Carbohydrate Metabolism in Health and Disease" were presented by four speakers at the June 2, 1983, NCC meeting. A summary of each presentation is given below.

   "Study of the Use of Starch in the Management of Glycogen Storage Disease" was presented by James Sidbury, M.D., Senior Scientist, Human Genetics Branch, NICHD:

Type I glycogen storage disease (GSD-I), an inherited absence or deficiency of hepatic, renal, and intestinal glucose-6-phosphatase activity, is associated with glycogen accumulation in these organs. The lack of hepatic glucose-6-phosphatase activity leads to hypoglycemia in fasting, because of the inadequate release of glucose from glucose-6-phosphate through normal glycogenolysis and gluconeogenesis. In recent years, continuous nocturnal infusion (CNI) of a glucose-containing solution provided either via a nasogastric or gastrostomy tube and frequent daytime feedings has been the preferred treatment for these patients. Although this treatment is generally effective, it requires monitoring of the night infusion as well as no delays in daytime feeds in order to avoid symptomatic hypoglycemia.

A study was done to determine whether giving patients with GSD-I uncooked oral cornstarch was an effective alternative regimen to CNI. Seven patients were treated successfully with the cornstarch for 4 to 20 months. After an optimal dose of cornstarch was determined, the patient was given cornstarch suspension without CNI and a diet consisting of 30-40 percent carbohydrate, and at least 2 grams/kg protein for 3 to 5 days. After testing the tolerance of the patients

for the different carbohydrates, i.e., dextrose, polycose and cornstarch, it was decided that the optimal dose of cornstarch was between 1.75 and 2.5 gm/kg. This dose produced a relatively constant blood glucose level (>70 mg/dl) for as long as 6 hours. Polycose and dextrose, however, resulted in an immediate rise followed by a rapid fall of glucose below 45 mg/dl (2.5 mmol/L.) within 3 hours. In one patient, polycose given every 4 hours resulted in a wide swing in blood glucose concentrations with levels falling as low as 24 mg/dl. It was apparent that the cornstarch regimen was as effective--if not more effective--than CNI for the maintenance of normoglycemia. The cornstarch suspension taken every 6 hours in doses ranging from 1.75 to 2.5 gm/kg/dose maintained normoglycemia in these patients.

When studied over time, the cornstarch regimen has been shown as effective as CNI for sustaining the commonly measured metabolic indices of adequate therapy in patients with GSD-I. These doses of cornstarch to maintain normoglycemia were equivalent to a rate of 5.3 to 7.6 mg/kg/min of glucose, which was less than that usually required for CNI (i.e., 8 to 10 mg/kg/min of glucose). The side effects of the cornstarch regimen have been minimal.

Oral cornstarch elicited a smooth blood glucose response if the initial blood glucose concentration was relatively normal. The cornstarch was less effective, however, if it was given when the blood glucose concentration was low. In addition, the use of cooked cornstarch or cornstarch suspended in hot water or lemonade resulted in a sharp rise in blood glucose followed by a rapid fall to hypoglycemic levels within 3 to 5 hours in GSD-I patients. The heating process may have disrupted the starch granules and made them more accessible to hydrolysis by amylase.

Pancreatic amylase and intestinal glucoamylase are the two primary enzymes responsible for starch hydrolysis. Levels of the former enzyme are negligible in the newborn period, however, they can be induced with oral starch. In patients with low levels of pancreatic amylase activity, CNI remains to be the therapy of choice.

Dr. Sidbury concluded that when glucose, polycose, rice starch, potato starch, cornstarch, cooked corn, cooked potato, and cooked rice with equivalent amounts of starch were compared in patients with GSD, cornstarch was found to be the most efficient in maintaining the blood glucose levels for the longest period of time. Cornstarch is therefore an important alternative therapy for the patient with GSD-I.

"Effects of Molecular Size of Dietary Carbohydrates on Metabolism" was presented by Bela Szepesi, Ph.D., Research Nutritionist, USDA:

Studies have shown that rats starved and refed diets containing high levels of carbohydrate have increased levels of hepatic dehydrogenase and lipid levels compared to rats fed diets ad libitum. Other studies have revealed that this increase in enzyme activity, especially of glucose-6-phosphate dehydrogenase (G6PD) and malic enzyme (ME) can

occur with lower levels of dietary sucrose than either glucose or fructose. The increase in G6PD above control levels is greater than the increase in ME. This sucrose effect cannot be explained entirely on the basis of the fructose moiety, since the sucrose diets contained only one-half as much fructose. It is quite possible that when sucrose is fed, the glucose moiety could repress gluconeogenesis and thus even further increase the lipogenic effect of fructose by reducing the gluconeogenic versus lipogenic antagonism.

In studies to examine whether the sucrose effect is due to a possible contaminant, rats were starved and refed diets containing 50, 40, or 31 percent glucose, fructose, invert sugar, sucrose, or brown sugar. Again, refeeding diets containing sucrose caused larger elevations in G6PD and ME activities than refeeding diets containing equal amounts of glucose. Refeeding 50 or 40 percent carbohydrate diets containing sucrose caused similar responses in each of the two enzymes whereas refeeding brown sugar, fructose, or invert sugar (made from equal amounts of glucose and fructose) resulted in G6PD and ME responses that were intermediate between the responses of glucose and sucrose-refed rats. Although near maximum enzyme induction occurred when rats were refed diets containing 50 percent carbohydrate, the sucrose effect was still discernible because refeeding sucrose (food grade) resulted in a statistically higher G6PD response than refeeding of either glucose or fructose diets. Both commercial sources of sucrose resulted in a statistically higher response of G6PD and ME than did glucose. Refeeding of food grade sucrose resulted in a significantly higher G6PD response than did laboratory grade sucrose. When compared with diets containing 50 percent white sugar, a diet containing 50 percent brown sugar resulted in an unusually low response of G6PD--a response that was significantly different from the response to food grade sucrose.

From these experiments it appears that a contaminant, either organic or inorganic, is not involved in the sucrose effect and that this effect is due in part or in total to a specific metabolic response to a disaccharide configuration of sucrose. In order to investigate this further, a study was conducted to determine whether the disaccharide effect is specific for sucrose and whether hepatic enzymes other than G6PD and ME also exhibit the disaccharide effect. A study was conducted to compare the effects of refeeding diets containing either 40 percent carbohydrate as monosaccharides (glucose, fructose, invert sugar) or disaccharides (maltose, sucrose) or 42.2 percent carbohydrate as glucose on hepatic enzyme activity. This study demonstrates that the disaccharide effect is not specific for sucrose, nor is it limited to non-reducing disaccharides or to disaccharides containing a fructose moiety. The enzyme responses to refeeding the carbohydrate diets fall into the following three categories: the disaccharide configuration of the carbohydrate and fructose increased the activity of G6PD, pyruvate kinase citrate cleavage enzyme, acetyl CoA carboxylase, and fatty acid synthetase; the disaccharide configuration of the carbohydrate alone increased G6PD and ME; and fructose increased the enzyme activity of phosphofructokinase and L-α-glycerolphosphate dehydrogenase. Refeeding diets containing 9equal molar amounts of glucose or maltose did not abolish the disaccharide effect.

Studies in which isolated intestinal cells from refed rats were used did not show a greater uptake of glucose when glucose was provided in the form of a disaccharide than when provided as free glucose. It appears that the disaccharide configuration of maltose and sucrose may have an effect at the gastrointestinal level which causes an increased induction of certain enzymes in the liver.

Studies to date indicate that the disaccharide effect is elicited by the presence of the disaccharide in the upper part of the small intestine. In a study of refeeding starved male rats with 40 percent disaccharides (maltose, trehalose, sucrose, or turanose), trisaccharides (melezitose), starch, or the monosaccharide equivalents, data indicate that G6PD and ME responses were greater with maltose, trehalose, sucrose, and turanose refeeding than with refeeding of their component monosaccharides. On the other hand, starch refeeding decreased the responses of glucose-6-phosphate dehydrogenase, malic enzyme, and fatty acid synthetase when compared to refeeding with glucose. No consistent correlation between portal blood carbohydrate concentration and liver enzyme levels could be demonstrated. For instance, while portal blood carbohydrate and liver enzyme levels were higher in rats fed maltose than in rats refed either glucose or starch, rats refed melezitose showed higher liver enzyme levels but lower portal blood carbohydrate levels than rats refed the monosaccharide equivalent of melezitose ("disaccharide effect"). A reduction, such as the enzyme-substrate specificity, is proposed--even the addition of one monosaccharide unit reduces or eliminates the "disaccharide effect."

In comparing the effectiveness of glucose, maltose, and starch to produce enzyme induction, the order of carbohydrates in descending order is maltose, glucose, and starch. Thus, the molecular size of the carbohydrate as well as the monomeric unit is important in determining the physiological response. Chemically sequestering glucose by the introduction of a soluble gum into the diet, such as xanthan gum, etc., or by the introduction of maltose into a lower part of the upper intestine, both reduce the enzyme response. Experiments to "fingerprint" free liver cells from rats fed various carbohydrates show that maltose causes not only increased lipogenesis, but also increased gluconeogenesis. Efforts will continue to attempt to isolate and characterize the disaccharide receptor.

Dr. Szepesi concluded that in starvation-refeeding regimens, dietary sucrose and maltose cause greater hepatic enzyme changes than diets containing their monosaccharide equivalents. The difference in enzyme response due to the feeding of the disaccharide could not be explained on the basis of contaminants, blood level of fructose, or the slight excess of carbohydrate contained in the disaccharide as compared to an equal mass of monosaccharide. Digestible disaccharides containing either glucose or glucose and fructose can produce the disaccharide effect. When the same disaccharide configurations are contained in a trisaccharide or polysaccharide configuration, the disaccharide effect can no longer be demonstrated. At present, there is no direct proof that disaccharides lead to increased rates

of diabetes or heart disease in animals or human subjects. However, the possibility that heart disease and diabetes rates might be reduced by substituting mono and oligosaccharides for disaccharides is worth investigating.

"Effects of Dietary Fructose in Hyperinsulinemic and Normal Men" was presented by Judith Hallfrisch, Ph.D., Research Nutritionist, USDA:

Fructose is becoming a major dietary ingredient in the U.S. due to the introduction of high fructose corn sweeteners and to the marketing of fructose for diabetics and dieters. Some research has shown that sucrose elevates blood lipids and increases insulin response in carbohydrate-sensitive individuals. And, fructose is the component of sucrose that may be responsible for some of these adverse effects on blood lipids.

One study included 12 carbohydrate-sensitive men selected due to their abnormally high insulin responses to a sucrose load and 12 men with normal responses. The mean insulin responses to the sucrose load were more than twice as high as the response found in the controls. Control subjects were matched to the hyperinsulinemic subjects by weight, height, age, etc. The diets given to the subjects followed a 5-day rotation and included 43 percent of the calories as carbohydrate, 15 percent as protein, and 42 percent as fat with a polyunsaturated/saturated fat ratio of 0.4. Calorie intake was based on the Recommended Dietary Allowances for body weight and consisted of 38 kcal/kilogram. These amounts approximated the average American diet according to the Nationwide Food Consumption Survey of the U.S. Department of Agriculture. In terms of calories, 15 percent were consumed at breakfast, 30 percent at lunch, and 55 percent at dinner. The three experimental diets contained exactly the same food with the exception of fructose or starch wafers; i.e., the 0 percent fructose diet contained 15 percent of the calories as starch, the 15 percent fructose diet contained 15 percent of the calories as fructose, and the 7.5 percent fructose diet contained 7.5 percent of the calories as fructose and 7.5 percent as starch.

After a 5-day equilibration period, the three experimental diets were each fed for 5 weeks in a crossover design. Initial body weight was maintained, blood samples were analyzed for plasma cholesterol and triglycerides every week, and a sucrose tolerance test was given at the end of each 5-week period.

The pretest values of total cholesterol and low density lipoprotein (LDL) cholesterol were significantly greater in the hyperinsulinemic men than in the controls. No initial differences were observed for high density lipoprotein (HDL) or very low density lipoprotein (VLDL) cholesterol, fasting triglycerides, free fatty acid response, or blood pressure.

After consuming the diets for 5 weeks, the hyperinsulinemic men tended to have greater--yet not significantly greater--total and VLDL cholesterol and lower HDL cholesterol levels than the controls. In

examining the combined groups of men, the total plasma cholesterol and LDL cholesterol were significantly greater when the men consumed 7.5 percent or 15 percent fructose than when they consumed 15 percent starch. Plasma triglyceride levels of the hyperinsulinemic men increased significantly as the level of fructose increased but were not significantly different from controls at 0 percent fructose. The level of fructose did not affect the triglyceride levels of the controls. Plasma glucose responses were higher when both groups of men consumed the 15 percent fructose diet than when they consumed the 0 percent diet. Total free fatty acid response or diastolic blood pressure were not affected by diet or type. The major effect of fructose on blood lipids was the increase in triglycerides. The differences observed in triglyceride levels between the two groups became more pronounced as the level of fructose in the diet increased indicating the greater sensitivity in the hyperinsulinemic men than the controls.

Fifteen percent of the calories as fructose can be considered an amount that could reasonably be expected to be consumed in this country. Although this level did not increase triglycerides in controls, it did elevate triglycerides to a mean level of above the normal 150 mg/dl in the hyperinsulinemic men. The increase in total cholesterol appeared significant with the increase in the LDL fraction, the major cholesterol fraction in the blood which correlates "more linearly" with heart disease than total serum cholesterol.

Dr. Hallfrisch concluded that fructose fed in moderate amounts in a normal American diet can produce undesirable changes in blood lipids that are associated with heart disease. Hyperinsulinemic men are more susceptible to these changes than controls. The changes include increased total plasma cholesterol, LDL cholesterol, and total plasma triglyceride. Thus, in view of the increasing amounts of fructose in the food supply, it is necessary to identify those persons considered susceptible to the effects of fructose.

"Effect of Dietary Sucrose on the SHR/N-corpulent Rat: A New Model for Insulin-Independent Diabetes" was presented by Otho E. Michaelis IV, Ph.D., Research Nutritionist, USDA:

The SHR/N-corpulent (cp/cp) rat strain was examined as a possible model for studying the etiology of obesity related insulin-independent diabetes, as well as the influence of dietary carbohydrates on this disease. The cogenic strain SHR/N-corpulent was developed by Dr. Carl T. Hansen, a geneticist at the Division of Research Services, by mating the obese hypertensive Koletsky rat that is heterozygote for the cp gene to a spontaneously hypertensive SHR rat. Twelve backcrosses were carried out to eliminate the noncorpulent genes of the Koletsky strain. Mating of the heterozygote corpulent rats yield three genotypes but only two phenotypes, i.e., homozygous (cp/cp) corpulent and heterozygous (cp/+) and homozygous (+/+) lean rats. The lean rats consist of 2/3 cp/+ and 1/3 +/+ rats.

The diets fed for 9 weeks to the 64 young male corpulent (cp/cp) and lean rats (cp/+ or +/+) contained 54 percent carbohydrate as either

sucrose or cooked cornstarch. Data on body weight after 4 and 9 weeks show that irrespective of phenotype, sucrose resulted in a greater body weight than starch (sucrose effect). A phenotypic effect (corpulent > lean) on body weight was also observed.

In terms of blood pressure, lean rats were moderately hypertensive after 4 weeks and markedly hypertensive after 9 weeks, whereas corpulent rats were normotensive. Hyperlipidemia was observed also in corpulent rats with fasting levels of serum total cholesterol and triglyceride 2 to 3 times greater than that in lean rats. Sucrose resulted in higher levels of serum lipids than did the starch in both phenotypes.

Hyperinsulinemia was observed in both phenotypes in the fasting and postprandial states with the corpulent rats markedly hyperinsulinemic and the lean rats moderately so. Serum insulin levels in the corpulent rat increased with age with sucrose affecting the insulin response.

A phenotype effect (corpulent > lean) was seen with fasting levels of serum glucose after 9 weeks, and with postprandial serum glucose after 4 and 9 weeks. The sucrose had a significantly greater effect on serum glucose levels of the corpulent rat than the starch. In addition, the sucrose fed corpulent rats had urine glucose concentrations twice that of the corpulent rats fed starch. Irrespective of phenotype, the sucrose resulted in greater urine volume than the starch.

This study demonstrates that the SHR/N-corpulent (cp/cp) rat develops an insulin-independent type of diabetes when fed a 54 percent carbohydrate diet and that the diabetic characteristics are greater when sucrose rather than starch is fed. The corpulent rats exhibited early onset obesity, hyperlipemia and hyperinsulinemia, and postprandial hyperglycemia and glycosuria. The lean rats were hyperinsulinemic but normoglycemic indicating insulin resistance.

The expression of diabetes in the corpulent rat appears to be associated with the high levels of serum insulin observed in the SHR/N-cp strain prior to developing obesity. The hyperinsulinemia is indicative of increased insulin resistance. Also, the diabetogenic stress of obesity, superimposed on an already insulin resistant genetic background, may also explain the occurrence of diabetes. The expression of diabetes cannot be related to hypertension since the corpulent rats are normotensive. Feeding sucrose to the corpulent rats further increases insulin resistance and the magnitude of the diabetic response.

Dr. Michaelis concluded that a diet effect (sucrose > starch) was observed with body weight, serum glucose response and urine volume in both corpulent and lean rats, and with fasting and response levels of serum insulin and total urine glucose in corpulent rats. Corpulent rats fed sucrose had 20 to 40 percent higher response levels of serum glucose and insulin and twice the amount of total urine glucose, than did corpulent rats fed starch. The data demonstrate that SHR/N-

corpulent rats (cp/cp) have metabolic characteristics associated with insulin-independent diabetes in humans and that sucrose is more diabetogenic than starch. Diabetes in this model appears to result from superimposing obesity on an insulin-resistant genetic background.

7. "The Nutrition Plan of the NCI" was presented by William DeWys, M.D., Associate Director, Prevention Program, Division of Resources, Centers and Community Activities (DRCCA), NCI, at the July 7, 1983, NCC meeting. A summary of his presentation is given below.

A planning process for the two NCI programs, the Chemoprevention Program and the Diet, Nutrition and Cancer Program, has been under way for the past 6 months with input from the staff of the Division of Resources, Centers, and Community Activities, the NCI Planning Office personnel, and members from other NCI Divisions. The goals of the chemoprevention program include identifying agents that have the potential to prevent cancer and to study them through pharmacological and toxicological tests before proceeding through clinical trials. A number of laboratory and epidemiological studies have shown that various agents can stop or reverse the progression of cancer in animals or reduce the incidence of cancer risk in humans. Two groups of potential chemopreventive agents that have been identified are: (1) the naturally occurring substances found in many foods and synthetic components considered safe for clinical trials (e.g. vitamin A, beta-carotene); and (2) agents currently undergoing intensive laboratory study but not yet ready for clinical trials such as the phenolic antioxidants, BHA and BHT, protease inhibitors, prostaglandin synthesis inhibitors, indoles and uric acid. Other dietary agents with a possible preventive effect include vitamins E and C, and selenium.

The diet, nutrition and cancer program focuses on food constituents and dietary patterns rather than on specific chemicals and nutrients. Both programs involve issues related to establishing efficacy, determining toxicity, and identifying mechanisms of action for the food or chemopreventive agent being studied. They also require the interaction of epidemiologists, clinicians and experimentalists with a mixture of investigator-initiated research and programmatic direction. In terms of planning, the studies under way as part of the two programs are evaluated at various stages in terms of specific criteria that must be met before moving to the next stage.

Issues important to these studies include timing in terms of the stage of carcinogenesis and whether an intervention impacts against the initiation or promotion phase, as well as the relevance of animal model systems that should be clarified through the planned sequence of animal and human studies. The epidemiological component of the studies considers the clinical, laboratory, and epidemiological investigations that may provide some clues to the potential of the agents or dietary factors to inhibit cancer. Clinical trials are set up in order to establish any cause and effect relationships and to define strategies of acceptable intervention for studies on diet and cancer or chemoprevention. The trials are composed of initial stud-

ies of intake and safety of a nutrient or chemical, pharmacological and biochemical factors, acceptability and compliance and long-term toxicity observations, as well as the eventual effectiveness in reducing cancer incidence or mortality. If the early stage studies prove to be successful, the intervention study is introduced into target populations with demonstration programs to monitor receptivity and toxicity. The application of this research to larger populations is considered if and when the population studies are successful. The set criteria used at this point includes issues of cost, acceptability and means for evaluation.

Dr. DeWys concluded that planning for these programs incorporates various decisionmaking stages that involve a decision committee and operating committees that are subgroups of the parent committee. These operating committees survey the results from each stage of the research and present this information to the decision committee. This committee reviews the results and decides whether an intervention should be passed on to the next stage, recycled in order to produce more critical information, or dropped from the program entirely.

8) "Should Diabetics Be Allowed to Eat Simple Carbohydrates?" was presented by John P. Bantle, M.D., Assistant Professor of Medicine, University of Minnesota, at the September 8, 1983, NCC meeting. A summary of his presentation is given below.

Recent data do not support the belief that dietary sugar (sucrose) aggravates high blood sugar in diabetics. For many years, it has been accepted that monosaccharides and disaccharides (such as sucrose) are more rapidly digested and absorbed than are complex carbohydrates such as potato and wheat starch, and thereby aggravate hyperglycemia. Studies now seem to indicate that diabetics do not need to be denied sucrose as long as weight reduction is not necessary and it is consumed in nutritionally balanced meals containing protein and fat. Including sucrose in the diabetic diet may increase overall dietary compliance and thereby help to achieve the goals of diet therapy.

Dr. Bantle's study, which included 10 healthy subjects, 12 patients with Type I diabetes (insulin dependent), and 10 patients with Type II diabetes (noninsulin dependent) who were each served a breakfast composed of common foods on five different mornings, pursued the issue of appropriate dietary feeding of carbohydrate to diabetics. Each breakfast contained nearly identical amounts of carbohydrate, protein, and fat with a different test carbohydrate (glucose, fructose, sucrose, potato starch or wheat starch) accounting for 24 to 25 percent of total calories and 50 percent of total carbohydrate calories. The meals varied from 685 to 742 calories.

The Type I diabetic patients, all of which had little or no ability to produce insulin on their own, were served breakfast exactly 30 minutes after administration of their usual dose of insulin and were not allowed to change the dose during the period of study participation. All Type II patients had fasting glucose plasma concentrations

greater than 140 milligrams/deciliter on more than one occasion or plasma glucose concentrations greater than 200 milligrams/deciliter at several time points after 75 grams of oral glucose.

The data from each of the three groups were analyzed separately with plasma glucose increments, or the difference in plasma glucose levels before and after each test meal calculated. Mean values were determined and an estimate of error was made using analysis of variance. In healthy subjects and Type I diabetics, the fructose meal produced the smallest mean peak increment in the plasma glucose level, while the glucose meal produced the greatest. These increments were significantly different in healthy subjects but not in the Type I diabetic subjects. The potato, wheat, and sucrose meals produced peak plasma glucose increments intermediate between fructose and glucose. These increments were not significantly greater than that observed with the fructose meal, or significantly lower than that observed with the glucose meal. In Type II patients, fructose produced the smallest mean peak increment in plasma glucose levels which was a significantly lower peak increment in plasma glucose than that achieved from potato, wheat, and glucose.

These data indicate that fructose produced the smallest mean peak increment in plasma glucose concentrations while glucose produced the largest mean peak increment in all three subject groups. Sucrose, potato, and wheat were intermediate in all three groups.

According to Dr. Bantle, a more important way to compare the effects of the test carbohydrate is to compare the "mean area increments" in plasma glucose concentrations after the five test meals. Using this method of analysis, in healthy subjects, fructose produced a significantly smaller mean area increment in plasma glucose concentrations than either wheat or glucose. Sucrose, potato and wheat produced a significantly smaller mean area increment than glucose. Again in Type I diabetics, none of the differences in mean area increments among the test carbohydrates were significant. In Type II diabetics, fructose produced a significantly smaller mean area increment in plasma glucose than sucrose, potato, wheat, and glucose. The data indicate that in all three subject groups, and of the five carbohydrates, fructose produced the smallest mean area increment in plasma glucose and glucose produced the largest mean area increment in plasma glucose concentrations. Sucrose, potato and wheat were intermediate.

Thus, the data do not support the previously accepted "dogma" that dietary sucrose aggravates high plasma glucose levels in diabetic patients. In both Type I and Type II diabetics, sucrose when consumed in a mixed meal with protein and fat did not produce a more rapid rise, a greater peak increment or a greater area increment in plasma glucose level than did comparable amounts of potato or wheat starch. The fructose fed produced less of an increase in blood sugar after a meal than the other test carbohydrates, however the differences observed were not statistically significant in Type I diabetic subjects.

Videotape Series, "Eat Well, Be Well II"

Following the wide public and professional acceptance of the first "Eat Well, Be Well" series, beamed in March 1981 to 225 Public Broadcasting System (PBS) television stations across the country, the NCC agreed to serve as consultants in a second production, "Eat Well, Be Well II." The second series, produced by Amram Nowak Associates with funds from the Metropolitan Life Foundation, is even more exciting than the first "Eat Well, Be Well" series since selected members of the scientific community participated along with Federal scientists. The series illustrates the successful collaboration of industry, government, and the scientific community in promoting public health.

"Eat Well, Be Well II," beamed by satellite in July 1983 to all PBS television stations, consists of 14 7-minute videotape segments that explain the role of nutrition in health promotion and disease prevention. Nine segments feature prominent physicians explaining the role of nutrition in health and disease. One segment features former DHHS Secretary Richard S. Schweiker explaining the importance of a regular exercise routine to health promotion. The series also includes a segment on "Body Weight," a segment by an Illinois farmer speaking on the production of low-fat meat, and an ethnic program with people of various backgrounds displaying the foods they commonly eat. Other segments address the issues of vitamins and minerals, carbohydrates, prenatal diets, milk and dairy products (and their relationship to osteoporosis), dieting, alcohol, fiber, vegetarianism, food substitution and cholesterol. Helen Hatton, home economist and chef in the "Eat Well, Be Well" series is again featured demonstrating appropriate recipes for the various nutrition topics. The theme song of the series emphasizes the role of proper nutrition and exercise in maintaining health.

This series, which is also available in 16 mm films, has been utilized with great success as a component of health fairs, as well as at organizational and scientific meetings. In FY 1983, the videotapes were featured as a major component of the NIH activities for National Nutrition Month, as well as at the First Annual DHHS "Health and Fitness Day" and other local health fairs. The series can also be used for nutrition instruction in primary and secondary schools, by church groups, and by any group interested in the role of nutrition in health and disease as well as the very important role of the combination of exercise and diet in maintaining health. The third "Eat Well, Be Well" series is in the planning stages.

Conferences Sponsored by the NCC

The NCC mandate calls upon the NCC to sponsor conferences, workshops, and symposia in areas of nutrition research that are of concern to the Institutes. In FY 1983, the NCC participated actively in the development of two conferences:

- The JSHNR's first annual "Conference of Federally-Supported Human Nutrition Research Units--An Information Exchange Activity of the JSHNR" was held in Washington, D.C., on December 16-17,

1982. The Directors of five USDA intramural nutrition research centers, the seven NIH Clinical Nutrition Research Units, and representatives of the intramural nutrition research program of the NIH, the nutrition research program of FDA, the nutrition research programs of the DOD, and the two nutrition research units supported by the AID presented highlights of their research programs. This conference is described in more detail with the activities of the JSHNR on pages 138-39.

- The "Satellite Conference on the Outpatient Management of Obesity," held October 2-4, 1983, in Washington, D.C. This conference was one of the six satellite conferences held in conjunction with the "Fourth International Congress on Obesity" on October 5-8, 1983, in New York City. The NCC Chairman attended several planning meetings and cochaired the satellite conference. The following issues were addressed: goals of treatment of obesity; prognostic factors (physiological and psychological) of obesity; assessment of motivation and compliance; integration of treatment modalities for obesity; characteristics of professional weight control programs; standards for professional weight loss clinics; cost:benefit analysis of outpatient management of obesity; third-party reimbursement for treatment of obesity: policy issues; and trends in research related to management of obesity.

SUBCOMMITTEE ON NUTRITION EDUCATION ACTIVITIES AND ACCOMPLISHMENTS

The charge of the Subcommittee on Nutrition Education is:

- To review NIH nutrition publications designed for the public
- To develop public service announcements
- Develop and implement National Nutrition Month activities at NIH.

In FY 1983, in accordance with its charge, the subcommittee reviewed the following nutrition publications intended for the public: "Facts About Cholesterol," developed by NHLBI; the revised version of "Facts About Nutrition," developed by NIADDK; and the public service announcement entitled "Nutrition and the Elderly," produced by NIA. The subcommittee also developed a comprehensive program of nutrition activities to be carried out at the NIH during National Nutrition Month, March 1983, and developed the NIH-NCC Nutrition Research Exhibit with its accompanying pamphlet, "Nutrition Research at the National Institutes of Health"; both these activities are described in more detail below.

In addition, the subcommittee continues to work with the GSI Cafeteria Service, through the NIH area manager, to introduce more nutritious food selections as part of the regular NIH cafeteria service. The GSI Cafeteria Service at NIH continues to feature the 'Eat Well, Be Well' salad bar complete with the calorie counts of the various salad toppings. A new service this year is a listing of the sodium

content of certain foods which are regularly available in the cafeterias.

In order to avoid duplication of effort and enhance the quality of the nutrition education materials destined for the public, the subcommittee has worked closely with the nutrition education staff of the CNRU's to collect nutrition materials prepared by the CNRU's and to provide the CNRU Directors and staff with information on nutrition publications and resources available from NIH and other agencies within the DHHS.

National Nutrition Month at the NIH (March 1983)

For the third consecutive year, activities to commemorate National Nutrition Month were held on the NIH campus during March 1983. The NCC and the Subcommittee on Nutrition Education cosponsored these activities, with the cooperation of the Recreation and Welfare Association (R&W), the Occupational Medical Service (OMS), and the GSI Cafeteria Service.

Due to the success of last year's theme, "MARCH FOR GOOD NUTRITION: Take Steps Against Disease," this theme was displayed again this year on posters in order to emphasize the role of nutrition in the prevention of diseases and conditions such as heart disease, high blood pressure, cancer, obesity, and other afflictions.

The activities featured throughout the month included scheduled viewings by the OMS of a film entitled "Weighing the Choices" which emphasized the effect of nutritional choices on overall health and well-being, as well as eight segments of the "Eat Well, Be Well II" videotape series.

The GSI Cafeteria Service provided NIH employees with nutrition information (such as calories and sodium content per serving) on certain food items as well as serving salt-free vegetables, a "Nutrition Month Salad Bar" complete with 12 topping choices, and a number of "National Nutrition Month Specials of the Day." Special tables were also set up in all cafeterias to provide NIH employees with the various NIH nutrition publications available to the public.

In order to emphasize the importance of a regular exercise routine, the R&W, with the assistance of the Maryland Commission on Physical Fitness, sponsored a program on employee office exercises designed to improve flexibility, minimize lower back pain, and help relieve muscle tension common to the work setting, and provided take home charts of the exercises.

NIH-NCC Nutrition Research Exhibit

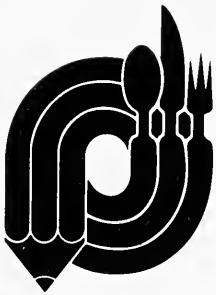
A major accomplishment of the NCC and the subcommittee was the development of the NIH-NCC Nutrition Research Exhibit and its accompanying pamphlet, "Nutrition Research at the National Institutes of Health." NCI, NHLBI, NIDR, NIAID, NIGMS, NICHD, DRR and the NCC office provided financial support for this activity.

The freestanding exhibit, designed to be displayed at scientific meetings and health fairs, provides the scientific community, health professionals, interested consumers and the general public with information on the NIH nutrition program. The exhibit illustrates the transfer of nutrition research from basic laboratory studies to clinical research, and the ultimate education of individuals on the role of nutrition in health promotion, disease prevention and disease treatment.

The exhibit's pamphlet provides descriptive information on the nutrition research programs of the 11 NIH Institutes and DRR, the names and addresses of the contact persons for the nutrition program within each Institute and DRR, as well as information on the application and review process for grants, projects, and training.

The NIH-NCC Nutrition Research Exhibit serves to illustrate the NIH commitment to nutrition research; helps to stimulate nutrition research along the lines of individual Institutes' program interests; and helps to encourage high quality applications for research projects in basic research, clinical investigation, and in the epidemiological aspects of nutrition science.

In FY 1983, the exhibit was first displayed at the annual meeting of the Federation of American Societies for Experimental Biology (FASEB), held in Chicago, Illinois, where it was enthusiastically received as evidenced by approximately 400 requests for the nutrition pamphlets available from the NIH, as well as for information on the NIH nutrition program. In addition, the exhibit, along with the "Eat Well, Be Well" videotapes, was featured at the Department's first annual "Health and Fitness Day," held at the Hubert Humphrey Building in Washington, D.C. Plans for FY 1984 are already under way to display the nutrition research exhibit at different national and international scientific meetings and health fairs.



III.

NUTRITION COORDINATING COMMITTEE OFFICE

The Nutrition Coordinating Committee office staff represents the NIH on a number of nutrition related committees involving other Federal agencies and departments. The staff was instrumental in the development and implementation of the Human Nutrition Research and Information Management (HNRIM) System as well as the Departmental 5-Year Plan for Human Nutrition Research and Training currently being developed under the auspices of the Developmental Research Initiative in Nutrition (DRIN). In addition, the staff is primarily responsible for responding to information requests about nutrition in general and about the NIH nutrition program in particular.

ACTIVITIES OF THE NCC OFFICE

As in past years, in addition to staffing the NCC and its subcommittee, the NCC office responded to a great number and variety of information requests on nutrition, nutrition research, and the NIH Program in Biomedical and Behavioral Nutrition Research and Training from a broad spectrum of sources, such as Congress and the General Accounting Office; the Executive Branch, including the Office of Science and Technology Policy, the Office of Management and Budget, and various agencies of the Public Health Service; as well as from the scientific community and the public. The central focus provided by the office has greatly facilitated NIH responses.

Since 1977, the NCC office has used a system for data retrieval of all nutrition research and training activities and expenditures of the extramural and intramural programs at the NIH that was computerized in 1979. This system has been used to develop reports on each Institute's nutrition program and on the overall NIH Program in Biomedical and Behavioral Nutrition Research and Training. In FY 1983, the NCC office was given the additional responsibility for developing the data storage and retrieval system that includes the human nutrition research activities supported by all Federal agencies represented on the Interagency Committee on Human Nutrition Research (ICHNR). This new system, called the Human Nutrition Research and Information Management (HNRIM) System operates out of the NCC office, was used to develop many of the tables and figures for this report and will be extremely helpful in responding to queries from Congress, the scientific community, and the public on the nutrition research supported by the Federal government. The HNRIM system is described in more detail on pages 133-35.

Other major responsibilities of the NCC office were: to compile and analyze the data on the NIH nutrition program in order to develop the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training; to prepare special reports as requested by Congress and other Federal agencies; to collect and analyze data in preparing testimony and "special presentations" for the Office of the Director (OD), NIH, the Office of the Assistant Secretary for Health, DHHS, and the Office of the Secretary, DHHS; to present the NIH nutrition program at national conferences and at meetings of professional societies; to assist the NIH/OD Information Office with the preparation of press releases; and to provide input into DHHS nutrition activities.

The NCC Chairman serves as the coordinator of the Departmental Research Initiative in Nutrition. Since 1978 the NCC office served as the Executive Secretariat for the Joint Subcommittee on Human Nutrition Research (JSHNR). The JSHNR was cochaired by the NCC Chairman and the Director of the Human Nutrition Center, USDA. The JSHNR was terminated on June 10, 1983, and has been succeeded by the Interagency Committee on Human Nutrition Research, which is cochaired by the Assistant Secretary for Health, DHHS, and the Assistant Secretary of Agriculture, Science and Education, USDA. The ICHNR has representatives from the same agencies previously represented on the JSHNR and has similar functions as the JSHNR. The NCC Chairman serves as the NIH representative to the ICHNR.

Congressional Hearings on Nutrition

In FY 1983, the NCC office staff provided input and was present at the hearing on the "Role of the Federal Government in Human Nutrition Research," held on July 14, 1983, before the Subcommittee on Science, Research and Technology of the House Science and Technology Committee and the Subcommittee on Department Operations, Research and Foreign Agriculture of the House Agriculture Committee. This was the third annual oversight hearing held jointly by the two subcommittees on nutrition research, and the purpose was: to determine the views of the Executive Branch and the public and private sectors on the role of the Federal Government in advancing the state of the art in human nutrition research; to ascertain present and future directions of nutrition research; to obtain justification for specific actions that appear to reduce the Federal role and responsibility in nutrition research; and to monitor the progress on the National Nutrition Monitoring System (NNMS), the Human Nutrition Research and Information Management System, and the Federal Human Nutrition Research Plan in order to determine if legislative initiatives or other actions are necessary to guide nutrition research coordination and policy.

The Assistant Secretary for Health, DHHS, testified on the planning and coordination of present and future directions in human nutrition research within the Department; the implementation of the HNRIM system and the work of the joint DHHS/USDA Task Force to have the system operational by FY 1984; and the implementation of the NNMS through the activities of the Nationwide Food Consumption Survey (NFCS), National Health and Nutrition Examination Survey (NHANES) Coordination Committee, the NFCS/NHANES Users Conference, and the Joint Nutrition Monitoring Evaluation Committee (JNMEC). The Assistant Secretary also testified that the seven "critical issues in human nutrition research and research training in the 1980's" which were identified in the JSHNR report "Federally-Supported Human Nutrition Research, Training, and Education: Update for the 1980's," have been useful in strengthening and coordinating the human nutrition research planning activities of the Department along with other mechanisms already in existence within the Department. He also noted the significant progress made in expanding the coordination and related nutrition activities with the U.S. Department of Agriculture (e.g., the coordination of the nutrition surveys of both Departments, the HNRIM system, and the establishment of the Interagency Committee on Human Nutrition Research). The Director, NIH, accompanied the Assistant Secretary for Health at the hearing and responded to questions.

Official Reports and Special Presentations on Nutrition

The NCC office provided information on the NIH and/or DHHS nutrition research activities for inclusion in reports prepared by the General Accounting Office, as well as reports prepared by other Federal agencies. In addition to numerous special reports, the NCC office annually supplies data used in the publication NIH Extramural Pro-

grams, which is a compendium of the scientific programs of the NIH components that award grants, cooperative agreements and contracts. The "Program in Biomedical and Behavioral Nutrition Research and Research Training" is included in the section on "Trans-NIH Research Programs."

Throughout the year, the NCC Chairman and office staff presented the NIH nutrition program and made special presentations on nutrition at the invitation of professional societies and other national and international groups interested in nutrition. In FY 1983, over 10 such presentations were made by the NCC Chairman before national and international organizations such as the American Heart Association's Committee on Nutrition; the Association of Children and Adults with Learning Disabilities; the scientific attaches of the European Economic Community; the Committee on Nutrition and Behavior of the International Life Sciences Institute; the Smithsonian Institution; and the National Nutrition Consortium.

In addition, the NCC Chairman represents the NIH on the following three DHHS Task Forces: the DHHS Task Force on Nutrition Objectives, the Interagency Task Force on Implications of the Infant Formula Code for the U.S., and the Task Force on the Assessment of the Scientific Evidence Relating to Problems on Infant Feeding. The report of the Task Force on the Assessment of the Scientific Evidence Relating to Problems on Infant Feeding will appear in Pediatrics in October 1984.

Human Nutrition Research and Information Management System

The NCC office staff, supported by the Division of Computer Research and Technology and in collaboration with USDA staff, through the USDA-DHHS Joint Task Force on HNRIM, under the auspices of the Joint Subcommittee on Human Nutrition Research and its successor the Interagency Committee on Human Nutrition Research, have developed the Human Nutrition Research and Information Management System, a computerized data base and information retrieval system that includes data on every federally supported nutrition research project.

The development of the HNRIM System began with the work of the NCC. Since 1977, the NCC has retrieved data on NIH projects with nutrition research and training components and their nutrition expenditures, based on the definition of human nutrition research developed by the NCC. The Joint Subcommittee on Human Nutrition Research, operating out of the Office of Science and Technology Policy in the Executive Office of the President, expanded the NIH definition and data collection system to include the human nutrition research activities supported by participating Federal agencies, and developed a system of 34 data classification categories for human nutrition research.

In December 1981, Congress mandated the Secretaries of Agriculture and Health and Human Services to formulate a plan for a Human Nutrition Research and Information Management System. Section 1427 of the National Agricultural Research, Extension and Teaching Policy Act of 1977 (7 U.S.C.-3177), as amended by Section 1425 of the National

Agricultural Research, Extension, and Teaching Policy Act Amendments of 1981 (Title XIV of P.L. 97-98) provides as follows:

> HUMAN NUTRITION RESEARCH AND INFORMATION MANAGEMENT SYSTEM
> Section 1427. The Secretary [of Agriculture] and the Secretary of Health and Human Services shall formulate and submit to Congress, within one hundred and eighty days after the date of enactment of this section, a plan for a human nutrition research management system. This system shall be based on on-line data support capability allowing for fiscal accounting, management, and control of cross-agency human nutrition research activities. The plan shall provide for management activities of all agencies managing funds for human nutrition research activities under existing authorities and contain recommendations for any additional authorities necessary to achieve a human nutrition research management system.

The Secretaries transmitted the plan to the Congress in July 1982. The plan states that:

> The Secretaries of Agriculture and Health and Human Services agree to cooperate in the development of a Human Nutrition Research and Information Management (HNRIM) System. The two departments propose to implement this plan with the advice and assistance of the Joint Subcommittee on Human Nutrition Research (JSHNR) of the Federal Coordinating Council for Science, Engineering and Technology (FCCSET). Initially the system will use the existing computer facilities of the HHS. However, existing computer facilities and systems supporting human nutrition research management in the Agencies are under review to determine the best long range approach to supporting the objectives of this management information system.

DHHS and USDA formed the Joint Task Force on HNRIM, under the aegis of the JSHNR, which was charged with: (1) reviewing the JSHNR data classification system; (2) defining the elements of the computer system; and (3) implementing the computer system. The Task Force reviewed and made slight modifications to the JSHNR classification system and developed a detailed data base. In FY 1983, the Task Force also prepared the first in a series of annual progress reports on HNRIM for submission to the Congress. The progress report described the development of the on-line data management system, and indicated that the data base and limited selection facility for on-line query would be available by October 1983.

The HNRIM system requires that each participating agency (at present DHHS, USDA, VA, AID, DOD, and DOC-NOAA) assemble and submit its own data; data from all participating agencies will be combined into the central HNRIM data base. The data base is to be updated quarterly, but can be updated more frequently if the need arises. The system provides convenient access to information on human nutrition research and research training activities supported in whole or in part

by the Federal Government. Fiscal data are limited to actual obligations (expenditures) by the originating Federal agency for the fiscal year in question and will not include state or private support. Federal pass-through funds are to be reported by the initiating agency. The information contained on each project in the data base includes: project identifier numbers, principal investigator, performing organization name and address, project title, sponsoring organization, congressional district, fiscal year, total funding, percent nutrition, nutrition funding, start data, nutrition classification categories, and a narrative description (abstract).

The system--which is "user friendly"--became fully operational in May 1984. On-line access to over 3,800 nutrition research projects supported by the Federal Government are available through the HNRIM system.

DHHS Research Initiative in Nutrition (DRIN)

In FY 1979, the NIH was designated as the sponsoring agency to develop the Nutrition Research Initiative, one of the DHHS Health Research Initiatives designed to focus on selected problem areas where mission needs of several DHHS agencies coincide with significant scientific opportunity. The agencies designated as cosponsors of the initiative were: NIH, ADAMHA, FDA, CDC, NCHS, and HRSA. The NIH-NCC Chairman was designated as the coordinator for developing the initiative.

The purpose of the nutrition initiative is to develop within the DHHS a more comprehensive and effective program of nutrition research and training to strengthen support of related missions. The principal thrust is to reinforce a coherent research program and to extend the growing trans-Institute cooperation in nutrition research to other DHHS agencies. A committee with members from the six agencies that conduct or support nutrition research and training has been given the task to develop a cohesive program for the Department in order to best carry out this initiative in nutrition research. This committee has the following responsibilities:

- o Review and comment on the plans, execution, and results of research efforts, in order to refine and strengthen the Department's nutrition program;
- o Coordinate research stemming from the obesity program, the CNRU's, nutrition research training and manpower development programs, and participation in OSTP's JSHNR (terminated in June 1983 and succeeded by the Interagency Committee on Human Nutrition Research);
- o Provide information and advice on the nutrition research program to the directors of the agencies involved, to the Office of the Assistant Secretary for Health, and to the Office of the Secretary;
- o Continuously evaluate research data and provide advice for the development of nutrition education materials for the public; and

- o Plan and arrange for conferences, workshops, consensus development exercises, and reports as appropriate.

Several conferences have been held and a number of major activities have been developed under the aegis of DRIN. Some highlights include:

- o The "Conference on the Assessment of Nutritional Status," where the Secretary, DHHS, inaugurated the DRIN with his keynote address. The conference was cosponsored by the NIH-NCC, CDC, and FDA and held at the NIH on September 16-18, 1981. The proceedings of this conference were published in the American Journal of Clinical Nutrition, May 1982 (Supplement), volume 35:1089-1325.

- o The "Workshop on Body Weight, Health and Longevity," cosponsored by NIH-NCC and CDC and held January 25-26, 1982. A review of the data and the conclusions of the workshop are described in a paper entitled "Body Weight, Health and Longevity" by Drs. Artemis P. Simopoulos and Theodore Van Itallie, that appeared in the Annals of Internal Medicine, volume 100, no. 2, February 1984.

- o The Joint PA, "NIH New Investigator Research Award (NIRA) in Nutrition: ADAMHA Special Notification for Research on Nutrition and Behavior," which marked the first time that NIH and another agency of the Public Health Service, ADAMHA, supported a Joint PA in nutrition. NIH and ADAMHA published a second Joint PA in March 1984, entitled "Studies on Obesity," which includes the research interests of NIADDK, NCI, NHLBI, NIA, NICHD, and NINCDS as well as NIAAA, NIMH and National Institute of Drug Abuse (NIDA).

Since 1979, the participating agencies of DRIN have provided data on their support of nutrition research to the JSHNR. In FY 1982, these agencies along with the other agencies and departments that made up the JSHNR, developed and agreed upon the HNRIM Classification System (described on pages 12-18). Subsequently, the participating agencies of DRIN, in collaboration with USDA and the other members of the JSHNR, were instrumental in the formulation of the HNRIM System Plan that was transmitted to Congress in July 1982. This effort has since been expanded to provide data on individual grants and projects for incorporation into the previously described HNRIM system.

At present, the agencies of DRIN are in the process of developing the Department's 5-Year Plan for Human Nutrition Research and Training, which will be included in the 5-Year Federal Plan for Human Nutrition Research and Training being developed by the ICHNR. NIH was assigned the lead responsibility for the coordination and development of the Public Health Service (PHS) portion of the plan. The NIH priorities for the 5-Year Plan appear in appendix F.

The Joint Subcommittee on Human Nutrition Research of the Federal Coordinating Council for Science, Engineering and Technology, Office of Science and Technology Policy, Executive Office of the President

In 1978, the Committee on Health and Medicine and the Committee on Agriculture, Food and Forestry Research of the Federal Coordinating Council for Science, Engineering and Technology (FCCSET), Office of Science and Technology Policy (OSTP), Executive Office of the President, established the Joint Subcommittee on Human Nutrition Research because of the vital importance of the benefits from human nutrition research to the welfare of the American people and the world population, and the need for nutrition research efforts of the Federal agencies to be mutually reinforcing. The membership included representatives from DHHS; OSTP; Department of Commerce, National Oceanic and Atmospheric Administration (DOC/NOAA); Department of Defense (DOD); Federal Trade Commission (FTC); International Development Cooperative Administration, Agency for International Development (IDCA/AID); National Science Foundation (NSF); United States Department of Agriculture (USDA); the Veterans Administration (VA); and in 1980, the National Aeronautics and Space Administration (NASA) was added. The JSHNR was cochaired by the NIH-NCC Chairman, who also served as Executive Secretary, and the Associate Administrator, Agricultural Research Service, USDA. The JSHNR was terminated on June 10, 1983, and has been succeeded by the Interagency Committee on Human Nutrition Research.

Over the years, the JSHNR has accomplished the following major tasks directed toward further enhancing coordination and improving planning of human nutrition research at the Federal level:

- Publication of three reports under the common title "Federally-Supported Human Nutrition Research, Training and Education: Update for the 1980's." These reports constitute the most thorough review of federally supported activities in human nutrition research ever undertaken and collectively represent an extensive review of Federal activities. The subtitles for this series were: "I. Human Nutrition Research and Training," "II. International Human Nutrition Research," and "III. Nutrition Education Research and Professional Personnel Needs for Nutrition Education of Professionals and the Public."

- Development of the HNRIM Classification System (see pages 12-18), based on the definition of human nutrition research (see appendix D) also developed by the JSHNR. The classification system consists of 34 categories that cover all aspects of nutrition research agreed upon and put into operation by all Federal agencies that support nutrition research. This classification system with minimal modification has been adapted for use by the Human Nutrition Research and Information Management System.

- Organization of the first annual "Conference of Federally-Supported Human Nutrition Research Units--An Information Exchange Activity of the JSHNR," held in Washington, D.C. on December 16-

17, 1982. The Honorable George E. Brown, Jr., Chairman of the Subcommittee on Department Operations, Research, and Foreign Agriculture, U.S. House of Representatives, delivered the keynote address at the conference. In his address, Congressman Brown said he was "somewhat surprised to learn that the components of Federal nutrition research management and planning were not in place prior to the establishment of the Joint Subcommittee."

In describing his views as to what constitutes a nutrition research plan, Congressman Brown said:

> A Nutrition Research Plan developed and accepted by representatives of the broad range of disciplines which encompass the science and application of nutrition would play a major role in advancing the state-of-the-art and emphasizing to policy makers and to the public the need for sustained and continuous support. The plan I envision is not intended to be a mechanism for controlling nutrition research or dictating specific research activities which would be pursued by the implementators. Rather, the plan should serve as a guide for directing and motivating research which would achieve comprehensive nutrition goals as defined by the leaders of the numerous disciplines which encompass the science and application of nutrition. The plan must be sufficiently flexible to tap the creativity of individuals, maintain the integrity of the scientific process and encourage centers of excellence.

The Directors of five USDA intramural nutrition research centers, the seven NIH Clinical Nutrition Research Units, and representatives of the intramural nutrition research program of the NIH, the nutrition research program of FDA, the nutrition research programs of the DOD, and the two nutrition research units supported by the AID presented highlights of their research programs. The 2-day conference concluded with a discussion of the need for continuous coordination and planning efforts by the JSHNR, and how professional scientific organizations, individual scientists, as well as foundations, may eventually be involved in the development of a National Nutrition Research Plan.

The first annual JSHNR conference provided the participants with first-hand information on the nutrition research priorities and activities under way at the various federally supported human nutrition research centers, and thereby established a solid basis for a thorough and exciting exchange of nutrition research findings and priorities. One important point stressed by the Directors of the Centers as well as other participants was the interdependence of all components of the Federal nutrition research effort and the need to keep open the channels of communication in order to stimulate continued cooperation.

Proceedings of the conference are being prepared for publication and will be made available in FY 1984 through the National Technical Information Service (NTIS).

- Preparation of a final report entitled "Federally-Supported Human Nutrition Research and Training: FY 1980 - FY 1982." This report, published in June 1983 was prepared in response to the recommendation made to and accepted by the Director, OSTP, that the JSHNR develop a Federal nutrition research plan by updating and expanding its December 1980 report. The report marks the completion of the subcommittee's work that focused on the identification and description of Federal nutrition research and training, the determination of critical issues in human nutrition research for the next decade, the development of recommendations regarding these issues and the enhancement of coordination of Federal human nutrition research programs. Thus, this report in conjunction with the three previous reports of the JSHNR forms the foundation upon which the Federal Plan for Human Nutrition Research will be proposed.

IV.
APPENDICES

APPENDIX A

MANDATE OF THE NIH NUTRITION COORDINATING COMMITTEE

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The Nutrition Coordinating Committee:

- Reviews and comments on the plans, execution, and results of pertinent Bureau, Institute, and Division research efforts relating to nutrition in order to develop the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training.

- Processes and responds to incoming requests for nutrition information from the DHHS and other Federal agencies, the Executive Branch of the Government, the Congress, outside institutions, and the public.

- Maintains up-to-date information on funding and on intramural and extramural research and training activities in nutrition.

- Develops and monitors means for improving the coordination of these activities.

Within the scope of the major activities described above, the NCC has the following specific functions:

- To define nutrition research at the NIH. (Accomplished, see page 3.)

- To develop a policy statement for research and training in nutrition at the NIH. (Accomplished, see page 147.)

- To establish information exchange. Each representative presents to the NCC any new plans, activities, conferences, and workshops that are concerned with nutrition. Future workshops and conferences are discussed to ensure full participation of all relevant Institutes; when many Institutes are involved, the NCC sponsors or cosponsors such workshops or conferences. Through the information exchange mechanism, the NCC identifies areas of collaboration for further research. The NCC informs the NIH nutrition community of all meetings, both within and outside NIH, concerned with nutrition. The committee, if requested, also reviews and comments on nutrition reports generated by the NIH and by other Federal and non-Federal agencies.

- To develop a data retrieval system for research and training in nutrition. (Accomplished, see page 4.)

- To review proposed legislation and regulations. The NCC develops mechanisms for receiving, reviewing, and distributing information on proposed legislation affecting nutrition policy.

- To develop and maintain effective liaison with other departments and agencies that have nutrition activities. The NCC assesses existing liaison mechanisms and identifies those departments and agencies requiring a liaison relationship. Liaison representatives

provide information to the NCC.

- To encourage the application of nutrition research to practice. The NCC members identify research data that are ready for "technology transfer" and promote the appropriate application of new knowledge in nutrition.

- To promote the dissemination of information for the purpose of public education on the role of nutrition on health and disease. The NCC assists in coordinating Bureau, Institute, and Division efforts in nutrition education and acts as a focal point for the dissemination of nutrition information to the public.

APPENDIX B

NUTRITION POLICY OF THE NIH

NUTRITION POLICY OF THE NIH

Policy Objectives:

The NIH supports DHHS policy by sponsoring and conducting biomedical research designed to improve the quality of life for all Americans through optimal nutrition. Basic biomedical nutrition research will develop knowledge needed to promote and maintain health, as well as to prevent and treat disease.

Nutrition research has passed through two stages and is now entering a third. The first stage saw the discovery of vitamins and the development of many of the basic nutritional requirements. The second stage reduced nutrition to subcellular and molecular terms within areas of biochemistry and physiology. The third stage calls for a synthesis of newer findings for translation into practical information to assist the individual to develop normally, to avoid disease, and to live as long and as healthy a life as possible. For this third stage, knowledge is needed that will permit distinction among individuals in terms of genetic differences that affect dietary requirements.

Areas of Emphasis:

Current nutrition research at NIH concentrates on eight critical areas:

1. Clinical Nutrition Throughout the Life Cycle. Research in this initial area examines variations in nutritional requirements to promote and maintain health during all phases of the life cycle. Within the clinical nutrition program, research is also directed towards elucidating the effects of infant feeding practices and infant nutrition on subsequent physiological, immunological, and mental development. Another research goal involving the life cycle is to understand the effects of maternal nutritional status and maternal diet before and during pregnancy on the development of the fetus. In order to understand the ramifications of this nutritional problem, more must be learned about the interaction between the genetic makeup of an individual and his dietary intake. Special emphasis is given to studies on the role of nutrition in health of the aged and aging process, particularly the effects of aging on nutrient utilization, digestion, absorption, and metabolism, and nutrition and age-related mental deterioration.

2. Role of Nutrition in Disease Development. The NIH conducts research on mechanisms by which dietary deficiencies, imbalances, and excesses lead to the development of physical and mental diseases and disorders.

3. Prevention of Disease. The NIH has assumed a leading role in shifting the emphasis in nutrition research from curing disease after symptoms have developed to preventing or delaying the onset

of disease. Continued research emphasis is given to malnutrition in all its guises, including under- and overnutrition, obesity, food faddism, and specific dietary deficiencies.

4. Treatment of Disease. The NIH develops nutritional therapies for specific diseases, such as cancer, gastrointestinal disorders, obesity, osteoporosis, renal insufficiency, atherosclerosis, and inborn errors of metabolism. Improved methods are being developed to provide general nutritional support for newborns of low birth weight who may require parenteral supplementation and for elderly, disease-ridden, traumatized, or postoperative patients who may require total parenteral nutrition or elemental diets.

5. Technology Transfer. An important component of the NIH nutrition policy is to assure appropriate application of research in practice. To expedite transfer of nutrition technology, the NIH is establishing mechanisms to evaluate research data relevant to nutrition and public health.

6. Nutrition Education. The NIH continues to support research in nutrition education as byproducts of clinical trials and demonstration projects; by the education of the physician through professional societies, scientific meetings, and journals; and by the production of nutrition education materials for the health educator and the public. Encouragement of positive nutrition behavior is an obvious task for educators of children, young adults, and the elderly.

7. Research Training. The NIH encourages and supports the teaching of modern biochemical nutrition at the pre- and postdoctoral levels. This training includes the disciplines upon which nutrition research is based, such as gastroenterology, endocrinology, metabolism, developmental biochemistry, genetics, and molecular biology. The NIH also promotes expanded training programs in basic and clinical nutrition research aimed principally at the physician investigator and clinically oriented biomedical scientists.

8. Coordination. The NIH cooperates in establishing mechanisms for interagency coordination. Nutrition research at the NIH is coordinated through the Nutrition Coordinating Committee. Institutes initiate their own nutrition programs within their appropriated budgets. The committee seeks agreement on critical issues of definition, comments upon individual programs identified to it, maintains an information exchange (mechanisms for program development), promotes liaison with other Federal agencies, and encourages coordinated program planning among Institutes and with other appropriate agencies. The committee assists in the development of nutrition data retrieval systems, and reviews legislative and regulatory initiatives that impact upon human nutrition research.

APPENDIX C

FY 1983 NUTRITION EXPENDITURES OF THE 11 INSTITUTES, DIVISION OF RESEARCH RESOURCES, AND FOGARTY INTERNATIONAL CENTER

TABLE C-1

National Cancer Institute
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	376	20,408		
	Clinical trials	119	1,613		
	Total			495	22,021
Program projects:	Regular	24	4,266		
	Clinical trials	3	1,085		
	Total			27	5,351
Contracts:	Regular	48	4,797		
	Clinical trials	12	438		
	Total			60	5,235
Centers:	Regular	29	1,923		
	Clinical trials	2	9		
	Total			31	1,932
Research Resources Support				0	0
Reimbursement Agreements				7	233
Research Career Development Awards				11*	269
New Investigator Research Awards				11*	299
Training:	Training grants	25*	577		
	Fellowships	0*	0		
	Total			25*	577
Subtotal - Extramural					$ 35,917
Intramural					
Projects				20	1,418
Training				0*	0
Subtotal - Intramural					$ 1,418
TOTAL NUTRITION RESEARCH AND TRAINING - NCI					$ 37,335

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-2

National Heart, Lung, and Blood Institute
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	135	13,784		
	Clinical trials	14	5,555		
	Total			149	19,339
Program projects:	Regular	14	5,572		
	Clinical trials	0	0		
	Total			14	5,572
Contracts:	Regular	5	1,224		
	Clinical trials	17	3,144		
	Total			22	4,368
Centers:	Regular	10	6,257		
	Clinical trials	0	0		
	Total			10	6,257
Research Resources Support				1	60
Reimbursement Agreements				5	384
Research Career Development Awards				7*	103
New Investigator Research Awards				9*	206
Training:	Training grants	136*	1,002		
	Fellowships	4*	55		
	Total			140*	1,057
Subtotal - Extramural					$ 37,346
Intramural					
Projects				10	952
Training				6*	52
Subtotal - Intramural					$ 1,004
TOTAL NUTRITION RESEARCH AND TRAINING - NHLBI					$ 38,350

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-3

National Institute of Dental Research
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	7	285		
	Clinical trials	0	0		
	Total			7	285
Program projects:	Regular	1	81		
	Clinical trials	0	0		
	Total			1	81
Contracts:	Regular	7	978		
	Clinical trials	0	0		
	Total			7	978
Centers:	Regular	1	209		
	Clinical trials	0	0		
	Total			1	209
Research Resources Support				0	0
Reimbursement Agreements				0	0
Research Career Development Awards				1*	33
New Investigator Research Awards				0*	0
Training:	Training grants	12*	233		
	Fellowships	2*	38		
	Total			14*	271
Subtotal - Extramural					$ 1,857
Intramural					
Projects				7	214
Training				0*	0
Subtotal - Intramural					$ 214
TOTAL NUTRITION RESEARCH AND TRAINING - NIDR					$ 2,071

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-4

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983, BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	347	22,916		
	Clinical trials	8	323		
	Total			355	23,239
Program projects:	Regular	9	2,056		
	Clinical trials	0	0		
	Total			9	2,056
Contracts:	Regular	2	122		
	Clinical trials	0	0		
	Total			2	122
Centers:	Regular	7	2,784		
	Clinical trials	0	0		
	Total			7	2,784
Research Resources Support				0	0
Reimbursement Agreements				0	0
Research Career Development Awards				11*	377
New Investigator Research Awards				22*	769
Training:	Training grants	67*	690		
	Fellowships	10*	164		
	Total			77*	854
Subtotal - Extramural					$ 30,201
Intramural					
Projects				24	2,820
Training				9*	311
Subtotal - Intramural					$ 3,131
TOTAL NUTRITION RESEARCH AND TRAINING - NIADDK					$ 33,332

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-5

National Institute of Neurological and Communicative Disorders and Stroke
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983, BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item	Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural				
Research grants: Regular	29	1,822		
Clinical trials	0	0		
Total			29	1,822
Program projects: Regular	6	521		
Clinical trials	1	21		
Total			7	542
Contracts: Regular	0	0		
Clinical trials	0	0	0	0
Total				
Centers: Regular	2	75		
Clinical trials	0	0		
Total			2	75
Research Resources Support			0	0
Reimbursement Agreements			0	0
Research Career Development Awards			0*	0
New Investigator Research Awards			3*	108
Training: Training grants	0*	0		
Fellowships	0*	0		
Total			0*	0
Subtotal - Extramural			$	2,547
Intramural				
Projects			0	0
Training			0*	0
Subtotal - Intramural				$ 0
TOTAL NUTRITION RESEARCH AND TRAINING - NINCDS			$	2,547

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-6

National Institute of Allergy and Infectious Diseases
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item	Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural				
Research grants: Regular	20	1,411		
Clinical trials	0	0		
Total			20	1,411
Program projects: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Contracts: Regular	1	23		
Clinical trials	0	0		
Total			1	23
Centers: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Research Resources Support			0	0
Reimbursement Agreements			1	10
Research Career Development Awards			1*	18
New Investigator Research Awards			1*	24
Training: Training grants	9*	9		
Fellowships	1*	18		
Total			11*	27
Subtotal - Extramural				$ 1,513
Intramural				
Projects			1	94
Training			0*	0
Subtotal - Intramural				$ 94
TOTAL NUTRITION RESEARCH AND TRAINING - NIAID				$ 1,607

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-7

National Institute of General Medical Sciences
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item	Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural				
Research grants: Regular	11	954		
Clinical trials	0	0		
Total			11	954
Program projects: Regular	1	194		
Clinical trials	0	0		
Total			1	194
Contracts: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Centers: Regular	4	606		
Clinical trials	0	0		
Total			4	606
Research Resources Support			0	0
Reimbursement Agreements			0	0
Research Career Development Awards			1*	0
New Investigator Research Awards			2*	44
Training: Training grants	79*	273		
Fellowships	1*	11		
Total			80*	284
Subtotal - Extramural				$ 2,082
Intramural				
Projects			0	0
Training			0*	0
Subtotal - Intramural				$ 0
TOTAL NUTRITION RESEARCH AND TRAINING - NIGMS				$ 2,082

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-8

National Institute of Child Health and Human Development
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	157	9,740		
	Clinical trials	10	1,129		
	Total			167	10,869
Program projects:	Regular	11	2,112		
	Clinical trials	3	1,437		
	Total			14	3,549
Contracts:	Regular	14	1,910		
	Clinical trials	1	319		
	Total			15	2,229
Centers:	Regular	11	614		
	Clinical trials	0	0		
	Total			11	614
Research Resources Support				3	48
Reimbursement Agreements				1	148
Research Career Development Awards				12*	247
New Investigator Research Awards				15*	617
Training:	Training grants	19*	268		
	Fellowships	9*	69		
	Total			28*	337
Subtotal - Extramural					$ 18,658
Intramural					
Projects				15	1,186
Training				32*	321
Subtotal - Intramural					$ 1,507
TOTAL NUTRITION RESEARCH AND TRAINING - NICHD					$ 20,165

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-9

National Eye Institute
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item	Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural				
Research grants: Regular	73	4,305		
Clinical trials	0	0		
Total			71	4,305
Program projects: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Contracts: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Centers: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Research Resources Support			0	0
Reimbursement Agreements			0	0
Research Career Development Awards			2*	48
New Investigator Research Awards			7*	171
Training: Training grants	0*	0		
Fellowships	2*	21		
Total			2*	21
Subtotal - Extramural			$	4,545
Intramural				
Projects			9	1,025
Training			0*	0
Subtotal - Intramural				$ 1,025
TOTAL NUTRITION RESEARCH AND TRAINING - NEI			$	5,570

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-10

National Institute of Environmental Health Sciences
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	11	907		
	Clinical trials	0	0		
	Total			11	907
Program projects:	Regular	1	483		
	Clinical trials	0	0		
	Total			1	483
Contracts:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Centers:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Research Resources Support				0	0
Reimbursement Agreements				0	0
Research Career Development Awards				0*	0
New Investigator Research Awards				0*	0
Training:	Training grants	0*	0		
	Fellowships	0*	0		
	Total			0*	0
Subtotal - Extramural				$	1,390
Intramural					
Projects				0	0
Training				0*	0
Subtotal - Intramural				$	0
TOTAL NUTRITION RESEARCH AND TRAINING - NIEHS				$	1,390

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-11

National Institute on Aging
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item	Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural				
Research grants: Regular	36	2,203		
Clinical trials	0	0		
Total			36	2,203
Program projects: Regular	9	1,416		
Clinical trials	0	0		
Total			9	1,416
Contracts: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Centers: Regular	0	0		
Clinical trials	0	0		
Total			0	0
Research Resources Support			0	0
Reimbursement Agreements			1	180
Research Career Development Awards			11*	87
New Investigator Research Awards			3*	67
Training: Training grants	30*	4		
Fellowships	1*	9		
Total			31*	13
Subtotal - Extramural				$ 3,966
Intramural				
Projects			5	425
Training			0*	0
Subtotal - Intramural				$ 425
TOTAL NUTRITION RESEARCH AND TRAINING - NIA				$ 4,391

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-12

Division of Research Resources
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Program projects:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Contracts:	Regular	1	1		
	Clinical trials	0	0		
	Total			1	1
Centers:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Research Resources Support				270	15,444
Reimbursement Agreements				0	0
Research Career Development Awards				0*	0
New Investigator Research Awards				0*	0
Training:	Training grants	0*	0		
	Fellowships	0*	0		
	Total			0*	0
Subtotal - Extramural					$ 15,444
Intramural					
Projects				0	0
Training				0*	0
Subtotal - Intramural					$ 0
TOTAL NUTRITION RESEARCH AND TRAINING - DRR					$ 15,444

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

TABLE C-13

Fogarty International Center
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1983,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Item		Breakdown Number	Breakdown Cost	Total Number	Total Cost
Extramural					
Research grants:	Regular	4	15		
	Clinical trials	0	0		
	Total			4	15
Program projects:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Contracts:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Centers:	Regular	0	0		
	Clinical trials	0	0		
	Total			0	0
Research Resources Support				0	0
Reimbursement Agreements				0	0
Research Career Development Awards				0*	0
New Investigator Research Awards				0*	0
Training:	Training grants	0*	0		
	Fellowships	3*	7*		
	Total			3*	7
Subtotal - Extramural				$	22
Intramural					
Projects				0	0
Training				0*	0
Subtotal - Intramural				$	0
TOTAL NUTRITION RESEARCH AND TRAINING - FIC				$	22

*Number of persons.
NOTE: The cost figures in this table reflect only research falling within the definition of nutrition research.

APPENDIX D

JSHNR DEFINITION OF HUMAN NUTRITION RESEARCH

Definition of human nutrition research

"Human nutrition research" is the pursuit of new knowledge to improve the understanding of nutrition as it relates to human health and disease and, as here defined, encompasses studies in three major areas: biomedical and behavioral sciences, food sciences, and nutrition education.

Research in the biomedical and behavioral sciences

Studies in the biomedical and behavioral sciences aspect of human nutrition research include: *1*) the consequences of food or nutrient intake and its utilization by the intact organism (animal model or human being); and *2*) the metabolic and behavioral mechanisms involved. Included are investigations of nutrient variables at the cellular or subcellular level. Also found here are:

- Dietary and nutritional studies expected to produce significant changes in the health status of humans, such as the maintenance of health and the treatment of disease. Such studies might take the form of clinical trials, epidemiological studies, metabolic studies, population surveillance, nutritional status monitoring, or efforts to evaluate various strategies for nutrition intervention and related public policies.
- Studies designed to explain the metabolic role or function of nutrients in humans and in animal models relevant to human nutrition.
- Studies concerned with genetic-nutrient-environmental interactions in humans, where a nutrient is an experimental variable.
- Studies of the interaction of diets and nutrients with toxic materials, manmade or naturally occurring, including drugs and carcinogenic agents.

Research in food sciences

Under the food sciences aspect of human nutrition research fall studies primarily concerned with the nutritional quality, content, or composition of foods, or with the bioavailability of nutrients in foods. Research activities related to the food sciences that are included in human nutrition research are:

- Studies on the nutritional characteristics of foods and diets for human use as influenced by various factors. These include varietal and species differences, harvest and postharvest technology, food processing, transportation, and retail food practices—when such studies are designed specifically to increase knowledge of human nutrition.
- Studies on methods to improve the speed and accuracy with which food components of nutritional importance are analyzed.

Research in nutrition education

Nutrition education research includes:

- Studies of dietary practices, food consumption patterns, and their determinants.
- Studies on methods for informing and educating the public about nutrition, health, and dietary practices.

APPENDIX E

LEGISLATIVE AUTHORITY OF NIH FOR HUMAN NUTRITION RESEARCH

LEGISLATIVE AUTHORITY OF NIH FOR HUMAN NUTRITION RESEARCH

Two Institutes have specific mandates to conduct nutrition research at the NIH. Those mandates are as follows (references to PHS Act):

NCI: Section 407(b)(4)--"Collect, analyze, and disseminate information (including information respecting nutrition programs for cancer patients and the relationship between nutrition and cancer) useful in the prevention, diagnosis, and treatment of cancer, including..."

NHLBI: Section 413(a)(1)--"investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences..."

Section 413(d)--"There shall be in the Institute an Assistant Director for Prevention, Education and Control...In the conduct of such a program, special emphasis shall be placed upon dissemination of information regarding diet, exercise, stress, cigarette smoking, weight control..."

Other Institutes that conduct and support nutrition research do so under much broader authority. Each conducts research programs in the "diagnosis, prevention, and treatment" of specific diseases and life processes within their areas of responsibility. Those authorities are as follows:

General authority	Section 301
International cooperation authority	Section 307
Training authority	Section 472(a)(1)(a)
NCI	Section 402(a)
NHLBI	Section 412(1)
NIDR	Section 422(a)
NIADDK	Section 434(c)
	Section 434(a)
	Section 439(a)
NICHD	Section 441(a)
NIGMS	Section 442
NIA	Section 464
Other Institutes	Section 431(b)

NCI LEGISLATIVE AUTHORITY FOR NUTRITION INFORMATION AND EDUCATION PROGRAMS

The specific mandates of the NCI for nutrition information and education programs are contained in Section 407(b)(4) of Public Law 92-218, "The National Cancer Act of 1971," as amended in Public Law 93-352, "Title I - Extension of Cancer Program":

> P.L. 92-218, Section 407(b)(4): "Collect, analyze, and disseminate all data useful in the prevention, diagnosis, and treatment of cancer, including the establishment of an international cancer research data bank to collect, catalog, store, and disseminate insofar as feasible the results of cancer research undertaken in any country for the use of any person involved in cancer research in any country."
>
> P.L. 93-352, Section 103: "Section 407(b)(4) of the Public Health Service Act is amended by striking out 'all data' and inserting in lieu thereof 'information (including information respecting nutrition programs for cancer patients and the relationship between nutrition and cancer).'"

NHLBI LEGISLATIVE AUTHORITY FOR NUTRITION INFORMATION AND EDUCATION PROGRAMS

The specific mandates of the NHLBI for nutrition information and education programs can be found in Section 413 of the Public Health Service Act, March 1977. This Section indicates the general plan for the Institute to expand, intensify, and coordinate the Institute's activities in the areas of heart, blood vessel, lung, and blood diseases and blood resources. To implement this mandate, Section 413(a)(1) states:

> "Investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases."

Section 413(d) states the following:

> "There shall be in the Institute an Assistant Director for Prevention, Education, and Control who shall be appointed by the Director of the Institute. The Director of the Institute, acting through the Assistant Director for Prevention, Education, and Control, shall conduct a program to provide the public and the health professions with health information with regard to cardiovascular and blood and pulmonary diseases and blood resources. In the conduct of such program, special emphasis shall be placed upon dissemination of information regarding diet, exercise, stress, hypertension, cigarette smoking, weight control, and other factors affecting the prevention of arteriosclerosis and other cardiovascular diseases and of pulmonary and blood diseases."

APPENDIX F

CRITERIA FOR PRIORITY SETTING AND PLANNING FOR NUTRITION RESEARCH AND RESEARCH TRAINING

AND

5-YEAR PRIORITIES FOR NUTRITION RESEARCH AND RESEARCH TRAINING BY INSTITUTE

CRITERIA FOR PRIORITY SETTING AND PLANNING FOR NUTRITION RESEARCH AND RESEARCH TRAINING

The first effort to coordinate nutrition research and establish criteria for priority setting at the Federal level in recent years occurred at the request of the Office of Management and Budget and the Office of Science and Technology Policy, Executive Office of the President, with the establishment, in April 1977, of an interagency working group. The group was chaired by the OSTP Assistant Director for Human Resources, with senior research staff representing Department of Agriculture; Department of Health, Education, and Welfare (DHEW, now renamed DHHS); Department of Defense; Agency for International Development; Office of Science and Technology Policy; and Office of Management and Budget. One of the responsibilities of the working group was to develop criteria for priority setting to be used by all the participating agencies. The following criteria were developed:

1. Importance of the Research: Why should it be given high priority; what would be the likely impact of the research--either directly on human health or on the ability to conduct other types of essential human nutrition research.

2. Specific Research Issues: What do we currently know; what do we need to know; what gaps in knowledge might the research effort fill; what are the specific goals for the research.

3. Researchability: Is it a tractable research task at this time--is there an adequate research capacity (knowledge base, methodology, skilled personnel, research techniques, facilities) to address the issue so that the research is likely to result in a significant breakthrough in knowledge. This criterion depends upon scientific judgements about methods available to operationalize research questions.

4. Present Level of Research: What is being done now or has been done recently in this area; what accomplishments to date; what is the funding level at present.

5. Proposed Activities: What is the minimum support level likely to produce results; what would be the incremental benefit of additional support; what is the likely funding requirement in 2 to 3 years and what personnel and facilities (Government and private sector) would be required at that time; what agency or agencies should be responsible for the work.

6. How Would the Research Be Conducted: What approaches would be used to conduct the research; would it be an extramural or an intramural effort, or both.

7. Coordination with Other Agencies: How would the research be coordinated with that being conducted by other agencies; what steps would need to be taken to ensure that the findings are most likely to be used by other agencies, by the medical community, by the nutrition and food science community.

Planning at NIH is a structured and integral part of the development and conduct of health research programs. The planning function establishes the framework through which goals, objectives, and research strategies are assessed, priorities set, resource allocations made, new programs developed and implemented, and existing programs modified.

Each Institute and Division has established its own planning process--and each responds to a common NIH process. These processes are designed to increase the probability that significant knowledge will be produced under a wide range of circumstances and will lead to safe and effective interventions in man. Underlying the planning of all research programs are a number of common points of reference:

- o assessment of the state of the art,
- o the scientific opportunities, and
- o the national significance of the problem.

Planning takes many different forms, depending upon the nature, scope, and context of the research activity being planned, the internal resources available, and the requirements imposed by legislation, organizational behavior, and management style of each Institute and Division. This variety of planning approaches reflects the great diversity and complexity in the many fields of inquiry that NIH supports, and in the processes through which knowledge is advanced.

The planning process of each Institute includes identification of program directions, establishment of research priorities, and consideration of resource allocations. While there are differences, each Institute must consider many similar factors in planning its programs. In general, each Institute annually:

- o assesses its goals, objectives, and the research strategies designed to meet those goals,
- o reviews program progress, the state of the art, evaluation studies, and various reports addressing particular program areas,
- o assesses scientific opportunities and plans program directions and emphases,
- o attempts to determine the national significance of health problems under consideration,
- o reviews program contributions to broader health goals established by the Public Health Service and DHHS,
- o reviews responsiveness of programs to congressional mandates, and

- o involves the Institute's National Advisory Council and the professional community in establishing program directions.

Consideration of these factors, in the form of planning documents, program reports, and discussions, provides the basis for recommending program changes to the NIH Director as part of the central NIH planning process.

The Division of Research Resources is unique at the NIH since it strives to assemble for the NIH-supported investigators throughout the academic and nonprofit institutions of our country a direct course for sustaining and enhancing the continuation of a high level national biomedical research resource enterprise. The task of determining which research resources are most needed to advance the knowledge-gathering and problem solving objectives of NIH investigators is a continuous challenge in the decisionmaking process of DRR. This process involves the biomedical community supported by the categorical Institutes and the private sector and two-way interaction with the categorical Institutes in order to interrelate broad NIH perspectives for appropriate decisions about research resource allocations and future directions.

In addition, many areas of scientific investigation, although component parts of the research of several Institutes, extend beyond the interests of individual Institutes. Trans-NIH coordinating committees have been used since 1977 as a structured method for devising proper research strategies in fields that are not restricted to the purview of individual Institutes. Nutrition is a prime example of such a research area. These areas are reviewed within the same structure as that provided for the individual Institutes, and each Institute with an interest in that particular area participates. For nutrition, all 11 Institutes, the Division of Research Resources, and the Fogarty International Center participate. Such review involves reports on the current status of planning, including assessment of coordinating mechanisms in place and future activities planned, as well as major issues that need to be addressed. If necessary, review sessions are scheduled with the Director, NIH, to discuss these matters.

The trans-NIH committees track research and the support of research in their field of study and advise administrators on the selection of areas of research emphasis, joint program announcements and awards, and research centers. The committees also sponsor symposia and workshops and endeavor to ensure coordination of efforts within NIH and cooperation with agencies outside NIH. Of all the trans-NIH committees, the Nutrition Coordinating Committee has consistently been the most active and effective in achieving these ends.

5-YEAR PRIORITIES FOR NUTRITION RESEARCH AND RESEARCH TRAINING BY INSTITUTE

NATIONAL CANCER INSTITUTE

Nutrition and Cancer

Scientific advances made over the past decade have revealed that approximately 80 percent of all cancers may be associated with personal lifestyles such as cigarette smoking, dietary habits, and occupation. Cancer is not an inevitable fact of life since many cancers can be prevented if people take the appropriate preventive measures. According to epidemiological studies approximately 30 to 35 percent of cancer deaths can be avoided through changes in dietary habits. For example, population studies have shown that an increased consumption of specific nutrients such as fat may be associated with an increased incidence of certain kinds of cancer. However, the correlation between diet and dietary components with certain forms of cancer does not mean causation.

Studies need to continue the investigation of the role played by certain diets, individual nutrients or food components including additives and contaminants in the initiation or promotion of carcinogenesis. More information is needed on the changes in nutritional requirements and/or utilization of aging normal cells related to or contributing to neoplastic change. Such changes in the immune system in cells and tissues may be modifiable through nutrition. Additional research is needed to increase our understanding of the role of nutrition in the causation, prevention and treatment of cancer.

Priorities for research in this area include:

- o Epidemiologic studies of associations between food groups or dietary factors and the incidence of specific cancers.
- o Studies of methods used for determining dietary and nutrient intake.
- o Studies of biochemical markers of dietary intake, susceptibility to disease and preneoplastic changes.
- o Studies of physical and chemical agents which cause cancer, compounds which inhibit or prevent cancer, and studies of the mechanisms by which these causative and preventive agents exert their effect.
- o Studies of immunomodulating effects (which may provide a defense against cancer) of nutrients and related chemicals.
- o Studies of the nutrient requirements of benign and malignant cells and the effects of tumor growth factors on nutrient requirements.
- o Clinical trials of specific dietary and nutrient interventions aimed at reducing the incidence of cancer.

- o Studies of the nutrient composition of foods and food groups relevant to the prevention of cancer.

- o Studies of the physiologic effects, metabolism, and potential toxicity of nutrients relevant to cancer prevention.

- o Studies of modification and control of eating behavior focusing on nutrients with cancer prevention potential.

- o Studies assessing the nutritional status of cancer patients and the metabolic effects of cancer.

- o Studies of the role of nutritional support in the treatment of cancer patients.

- o Studies of transmission of information to cancer patients and to the general public and the impact on level of knowledge, attitudes and behavior.

Nutrition and Immunology: Infection

Additional research is needed to increase our understanding of the role of nutritional status and specific nutrients on immunologic determinants of susceptibility and resistance to various cancers.

Priorities for research in this area include:

- o Studies of the immunomodulating effects of nutrients and related chemicals which may provide a defense against the development of cancer.

- o Studies of the effects of nutrition on the function of host defenses in patients with immunodeficiency diseases who are more susceptible to cancer.

- o Studies of the effects of nutritional status and specific nutrients on defenses against infections in patients who have cancer.

NATIONAL HEART, LUNG AND BLOOD INSTITUTE

Nutrition and Heart and Vascular Diseases

Current and continuing research will include the emphasis on nutrition research related to atherosclerosis, hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, and chronic heart failure. The scope of such research includes all aspects of the biomedical research spectrum from basic research to demonstration and education research.

Additional studies are required to advance our knowledge on the role of nutrition in the etiology, prevention, and reduction of morbidity and mortality from the cardiovascular diseases.

Priorities for research in this area include:

- Studies of nutritional interventions to prevent recurrences of cardiovascular diseases or delay progression of these diseases in individuals with diagnosed cardiovascular diseases.

- Studies of nutritional interventions to prevent or delay the onset of clinical disease in populations that have a high risk of coronary heart disease or hypertension, with a primary research focus on prevention in the young.

- Establishment of a NHLBI Nutrition Data System to develop and improve methods for data collection, to code and characterize the nutrient content of diets, to maintain current food composition tables and to train personnel in nutrition data collection techniques.

- Research into the roles of nutritional factors and hypertension, such as sodium, potassium, chloride, calcium, magnesium, polyunsaturated fatty acids, proteins, amino acids, and carbohydrates, and other factors such as the role of obesity, caloric intake, alcohol intake, and trace elements.

- Further studies of the independent effects and interaction of dietary sodium and potassium, weight changes, physical activity, and "relaxation" methods in the control of borderline and mild hypertension and their contribution to conventional antihypertensive therapy.

- Investigations to elucidate the mechanism of hypertensive effects of obesity that may be mediated through various concomitant metabolic changes, for example, sodium retention and hormone metabolism.

- Continued studies of the effects of sodium loading in salt sensitive and control individuals, including infants, twins, and families.

- Comparative studies on the effects of vigorous nonpharmacologic control in hypertension and as a component of treatment in step-down tests of drug therapy.

- Further studies and additional analysis of existing data on the side effects, especially long-term, of blood pressure medications, including effects on blood lipid-lipoprotein levels, glucose tolerence and insulin sensitivity, on exercise performance, etc., and the role of nutrition in prevention or control of these side effects.

- Studies to determine more effective LDL-lowering and HDL-raising dietary regimes by changes in total calorie intake and component nutrients, including factors such as vegetable protein, levels of saturated and unsaturated fatty acids, specific fatty acids, amino acids, fiber, complex carbohydrates, and polysaccharides, with and without the added effects of weight loss and increased physical activity.

- Prospective epidemiological studies of nutritional factors in relation to coronary atherosclerosis, cerebrovascular disease, and hypertension.

- Continued investigations of the apparent paradox between low order correlations of obesity and overweight and CHD; of the influence of long-term gain and loss of weight; of the interaction of heredity and environment in obesity; of the mechanisms by which obesity influences blood pressure and blood lipids; and of weight control programs designed to meet the needs of varied population groups, especially minorities and socially disadvantaged.

- Studies of the effectiveness of multiple risk factor modifications, e.g., changes in blood lipids and lipoproteins, blood pressure, and physical activity as alternatives or as adjuncts to pharmacologic and surgical therapies in survivors of myocardial infarction.

- Randomized studies to determine the influence of multiple risk factor modification, including nutrition, on subsequent morbidity and mortality in patients who have undergone coronary artery bypass surgery or percutaneous transluminal coronary angioplasty.

- Studies of education strategies, methods, and materials compatible with use in ambulatory health care settings to achieve effective blood lipid modification and long-term dietary change.

- Research to determine the effectiveness, feasibility and cost of nutritional counselling within present health care settings.

- Studies to test the effectiveness of risk factor interventions, including nutrition, on primary care physicians' cardiovascular risk factor management procedures in office-based practices.

- Research to identify the characteristics of the worksite population that determine levels of participation in nutrition and other

cardiovascular health promotion strategies, and on the interaction of nutrition worksite efforts with community-wide programs as a determinant of responses by different subgroups.

- o Studies of factors that contribute to school health promotion and the establishment of nutrition and physical activity behaviors.

- o Studies of the short- and long-term effects of nutrition education within school health programs to identify those methods that are effective for changing behaviors and risk factor levels.

- o Research to determine the variables related to the diffusion of health promotion programs in schools and to analyze the effectiveness and cost of dissemination of such programs.

- o Studies to examine the interaction of classroom health education curricula with school-wide and community-wide programs, including measurements of the relative effects on knowledge, attitudes, behavior, and physiologic risk factor levels.

- o Research to develop test instruments that measure awareness, attitudes, and behavior related to cardiovascular risk factors, including nutrition in youth, for application to education.

- o Longitudinal research to identify the development stages in the acquisition of positive and negative cardiovascular health behavior, including socioeconomic and ethnic variables; to identify the optimal ages and health education strategies for teaching CVD health promotion; to examine the interrelationships of the family, peers, media, community organizations, school health services and lunch programs, school environment, health curriculum, and teachers at the different development stages.

- o Research in the special problems of nutrition in the elderly as related to the management of cardiovascular disease, including the nutrient intake as related to CVD health in elderly populations.

Nutrition and Blood Diseases

A major focus of nutrition research in blood disease is the sickle cell disease research in which the influence of nutritional factors on red cell physiology and the contribution of vitamin and mineral deficiencies to growth retardation and immunofunction are being studied.

Priorities for research in this area include:

- o Studies to elucidate the role of nutritional factors in mechanisms that influence the clinical manifestations of sickle cell disease.

- o Studies to identify the effect of nutrition on delayed or impaired development and growth in children with sickle cell anemia.

- Studies into the potential role for nutritional supplementation to correct deficiencies and improve growth in children with sickle cell anemia.

- Research on a possible nutritional etiology for the immune dysfunction in patients with sickle cell anemia.

- Further investigation of the subset of pediatric patients with sickle cell anemia who fail to thrive with normal caloric intake in order to determine whether this represents increased caloric turnover, decreased absorption or a hypermetabolic state. A trial period of hyperalimentation in these patients may be of value in correcting this "failure to thrive" syndrome.

- Studies to establish a systematic approach to assessing the nutritional status of patients as part of the management of patients with sickle cell anemia. Methods to assess nutritional adequacy must be evaluated and data obtained to define this problem as it relates to sickle cell anemia. A nutritional assessment is important to the comprehensive approach to patient management with appropriate dietary supplementation and techniques developed to monitor the outcome of nutritional intervention.

Nutrition and Lung Diseases

The effects of nutrition have not been studied as extensively in the lung as in other organs such as liver, muscle, brain and bone. Thus, both basic and clinical experimentation have potential for increasing our understanding of the role of nutrition in the etiology, pathogenesis and management of pulmonary disease.

Priorities for research in this area include:

- Investigations into the role of nutrition in the management of chronic obstructive pulmonary disease including the relation of nutrition to the course of the disease, to respiratory muscle strength, and to respiratory failure.

- The role of nutritional status in influencing the course of lung development and of pediatric pulmonary diseases, with emphasis on the role of vitamin A, vitamin E, and essential fatty acids in infants with respiratory distress syndrome.

- Studies of the effect of nutritional status on lung metabolic and defense functions in the adult and developing lung.

- Studies of the influence of dietary antioxidants such as ascorbate and other nutrients such as cysteine, selenium, vitamin B_6 and vitamin E in the protection of the lung from oxidant injury.

- Studies to develop improved methods for administering nutrient support to patients with pulmonary disorders.

NATIONAL INSTITUTE OF DENTAL RESEARCH

Nutrition and Oral Health

Periodontal diseases include inflammatory conditions that affect the tissues around the roots of the teeth and lead to tooth loss. Dental caries affects the majority of the American population and is the leading cause of tooth loss in children and adults. Recent surveys indicate that the prevalence of coronal caries among children has decreased during the last decade, probably because of the widespread application of fluorides; however, two-thirds of the Nation's school children suffer from the disease. Little is known about secondary caries and root caries, which affects adults and may be increasing in prevalence. Additional research is needed if the disease is to be eliminated as a public health problem. Fundamental and clinical research needs to be conducted on the etiology, pathogenesis and prevention of dental caries.

Priorities for research in this area include:

- o Studies to define "critical periods" of development for each oral tissue in terms of the nutrients required to assure optimal structure and function of the tissue.

- o Studies to identify nutritional factors that affect orofacial growth and development and host defense factors known to be important in preventing oral diseases.

- o Investigations of nutritionally caused defects at the cellular and molecular levels.

- o Studies to determine the role of nutritional factors and nutrients in the maintenance, functioning and repair of oral tissues.

- o Investigations to identify optimal levels of specific nutrients in oral tissues to assure maintenance and functional relationships between nutrition and hormonal interactions, specifically in tissue responses to infection and injury; and contributions of marginal or conditional nutritional deficiency states to the etiology and pathogenesis of oral diseases and disorders.

- o Studies to identify nutritional factors affecting salivary gland function.

- o Studies on the protein components and enzymatic activities of saliva, the buffering capacity of saliva, and the immune response of the salivary glands in relation to overall nutritional status and particular nutrient requirements.

- o Studies to examine changes induced by nutritional deficiencies, excesses, or imbalances in relation to their effects on saliva-plaque interactions.

- Studies to examine the relationship between osteoporosis of the mandible and periodontal diseases.
- Studies to characterize the relationship between nutrition and both the immune and nonspecific defense mechanisms of the periodontium.
- Investigations to determine the effects of specific nutrients on the initiation of gingivitis, utilizing a short-term human model.
- Studies to determine the relationship of dietary intake to caries incidence.
- Studies to identify food components with anti-cariogenic properties.
- Clinical trials to determine if prenatal fluoride supplements are a potential caries preventive method.
- Pharmacological studies on intraoral fluoride-releasing device.
- Studies to determine the effects of severe fluorosis on oral health.
- Clinical trials to determine the efficacy of adult fluoride mouth rinses.
- Studies to characterize the relationship between nutrition, aging, and oral health.
- Investigations to determine the extent to which inadequate masticatory ability compromises nutritional status by altering food intake.
- Studies to evaluate the impact of optimal nutrition on age-related changes in oral tissues or salivary gland function.

NATIONAL INSTITUTE OF ARTHRITIS, DIABETES,
AND DIGESTIVE AND KIDNEY DISEASES

NIADDK fosters and supports research in the broad areas of fundamental and clinical nutrition. Application of the recent state-of-the-art techniques in the areas of cell biology, molecular biology, immunology, and integrative physiology is encouraged in order to increase knowledge concerning: (1) the function and requirements of nutrients, (2) the relationship of diet (and nutrients) to health and disease, and (3) the prevention and treatment of diseases as an outgrowth of nutrition research. The fundamental research supported by NIADDK generally has been nutrient-centered rather than focused on a particular disease, organ, or life cycle state. In contrast, the clinical investigations usually concern problems of interrelating nutritional status with the biochemical and physiological function of cell populations, organs or the whole individual. Clinical problems of interest to NIADDK include obesity, anorexia nervosa, diabetes, chronic renal disease, end-stage liver disease, gastrointestional dysfunction, bone disease, total parenteral nutrition, and combined nutrient-drug interactions and management of patients.

Nutrition--General

Research in human nutrition is an interdisciplinary and complex endeavor in integrative physiology. Clinical nutrition research requires the close interaction of several basic biomedical research disciplines and clinical specialties. Important questions which are of interest include establishment of optimal, as well as minimal, nutrient requirements in health, disease and notably in the prevention of diseases and disorders. Little is known about the effects of stress, drug use, toxicants, nutrient imbalance, activity level, food consumption patterns, disease states and other environmental and host factors on nutrient requirements and interactions in man. Thus, studies are needed to examine the physiological function and mechanisms of action/interaction of essential nutrients within the body, i.e., studies to examine the bioavailability of nutrients, their digestion, absorption, and transport by the GI tract at the cellular and subcellular levels.

Priorities for research in this area include:

- o Investigations on environmental, genetic and host factors which may influence human nutrition requirements such as bioavailability, nutrient imbalance, drugs, disease, stress, activity level.

- o Studies on physiological function of essential nutrients in health and disease, with emphasis on amino acids, calcium, magnesium, trace elements and vitamins, and including understanding the mechanisms of function at the cellular and subcellular level.

- o Research to explore the significance of proportion and amount of macronutrients (dietary protein, fat, and carbohydrate) in control of metabolism and cellular function in health and disease, as well as its role in disease prevention.

- Research on the significance of type and amount of dietary fiber in health and disease.

- Studies on the basic, clinical and behavioral aspects of obesity including problems of genetic variance and induced metabolic change.

- Research on the nutritional support of patients with special interests relating to long-term total parenteral nutrition.

- Studies to improve methods of assessment of nutritional status and dietary intake.

- Studies on the role of nutrition in infection and immune competence.

- Investigations to examine nutrient-hormone interaction in the regulation of bone metabolism.

- Studies on the nutritional aspects of diabetes and other endocrine and metabolic disorders.

- Research to foster a multidisciplinary approach to clinical nutrition problems.

Nutrition and Digestive Diseases

The digestive tract is a complex system of organs responsible for converting the food we eat into the nutrients we need to sustain our bodies. Although the relevance of the functions of the digestive tract to nutrition and to the general health status of the individual seems quite apparent and straight forward, the specifics of the relationships have not received as much attention by biomedical investigators as would be expected. With the increasing utilization of enteral and parenteral nutritional support of the patient, important differences brought about by the route of delivery of nutrients (parenteral, oral, gastric, duodenal or jejunal delivery) can be investigated.

Priorities for research in this area include:

- Investigations to ascertain the role of different constituents of dietary fiber in diseases such as gallstones, irritable bowel syndrome, inflammatory bowel disease, diverticulosis and colon cancer.

- Studies to examine the effects of dietary fiber on the release of hormones by nerve cells in the GI tract.

- Studies to explore the effects of release of GI hormones on control of appetite, rate of gastric emptying, intestinal motility, and gut-brain interactions.

- Studies to explore the effects of hormones secreted in the GI tract on growth and development of gastrointestinal tissues and their functions.

- Investigations to examine the effects of gastrointestinal motility on nutrient absorption.

- Studies to consider the possible relationship between specific foods or nutrients and gastric acid secretion.

- Studies to examine the differences in nutrient absorption between oral and tube delivered foods.

- Studies to examine the differences in metabolism of nutrients when given parenterally or enterally.

- Examinations to explore the influence of intestinal microflora on human nutrition.

- Investigations to examine the immunological and allergic responses to foods by the intestinal immune system.

- Studies to examine the physiological and biochemical alterations of gastrointestinal tract function with aging affecting nutrient delivery and metabolism.

Nutrition and Renal Disease

The kidneys are vital organs critical to the maintenance of the body's internal environment, particularly in terms of the composition, volume, and pressure of the body fluids. Research examines not only kidney physiology, but also the risk factors for kidney disease and the factors responsible for the varying rates of progression of renal disease to end-stage renal disease, one of the Nation's major public health problems. To date, the mechanisms of this progression and the roles of contributing factors such as dietary protein and hormonal action remain unclear.

Cardiovascular complications are among the leading causes of premature death in end-stage renal disease patients on maintenance hemodialysis therapy. As in non-uremic individuals, exercise training has been associated with beneficial effects on many coronary risk factors.

Priorities for research in this area include:

- Studies to ascertain the influence of dietary protein restriction on the rate of progression of chronic renal disease/renal insufficiency.

- Studies to ascertain the influence of dietary phosphate restriction on the management and prognosis of chronic renal failure.

- o Studies to ascertain the pathophysiologic mechanisms to explain the effects of dietary metabolic alterations of kidney disease.

- o Investigations to examine the effects of high protein diets on renal function and structure in health and disease.

- o Studies to ascertain the interrelationships of dietary protein intake, diabetes mellitus, and hormonal actions on the progression of renal disease.

- o Studies to elucidate the basic mechanisms leading to improved glucose and lipid metabolism which occur in association with exercise in patients on hemodialysis.

- o Investigations on trace element disturbances (both deficiencies and excesses) that occur in uremic patients as a consequence of altered renal function and/or dialysis.

Nutrition and Endocrine and Metabolic Disorders

The nutritional status of the individual has an influence on the development and function of the various endocrine organs. Altered nutritional status by itself or through consequent abnormalities of an organ system can also result in metabolic disturbances. Nutrient supplementation both at physiological and pharmacological levels has become an integral part of the therapeutic intervention of several inborn errors of metabolism. At the same time, the study of a number of inborn errors of metabolism has provided significant contributions to our understanding of the metabolic fate or function of various nutrients, especially vitamins and their metabolites.

Priorities for research in this area include:

- o Studies to examine the neuroendocrine control of organ and body growth, food intake, satiety and energy balance.

- o Studies to examine the alterations of endocrine function as a consequence of fasting, bulimia, obesity and anorexia nervosa.

- o Examination of dietary habits in the control of diabetes.

- o Investigations to examine the pathophysiological relationships between diabetes and obesity.

Nutrition and Musculoskeletal Diseases

Osteoporosis, a condition in which bone tissue decreases, is a major chronic disease of older people, especially women. Between 2 and 5 million Americans seek medical help each year for some problem linked to osteoporosis and upwards of 15 million have osteoporosis to some degree. The disorder is eight times more common in women than in men and in most cases the women are in their fifties or sixties. Women who have passed menopause are especially vulnerable because changes in the body's hormone levels accelerate loss of bone tissue. As

estrogen levels decrease, calcium available from foods is not as easily absorbed and calcium from the bones is more likely to be used by the body for other needs.

Various clinical trials with dietary and hormonal treatment modalities either singly or in combination are being conducted. New proteins have become recognized that appear to regulate bone mineralization. Mechanisms of interactions between these regulators of bone metabolism and nutrient availability need to be better understood for application to both prevention and management of bone disease and fractures.

Priorities for research in this area include:

- o Studies to ascertain the influence and interaction of fluoride, calcium, vitamin D metabolites and estrogen supplementation in osteoporosis.

- o Studies to ascertain the mechanisms of action and interaction of fluoride, calcium, vitamin D metabolites and estrogen in the treatment of osteoporosis.

- o Studies on nutritional factors controlling the mineralization process of bone.

Nutrition and Skin Diseases

Oral retinoids appear to be a promising group of agents in the treatment of various skin conditions such as psoriasis and keratinizing disorders. Recent case reports indicate retinoids may be useful in other diseases such as lupus erythematosis. Consequently. further research is needed in order to determine the mechanisms by which these agents work.

Priorities for research in this area include:

- o Studies to elucidate the biochemical and pathophysiologic mechanisms by which retinoids work in suppressing acne and affect keratinizing disorders.

NATIONAL INSTITUTE OF NEUROLOGICAL AND
COMMUNICATIVE DISORDERS AND STROKE

Nutrition and the Nervous System

In order to better understand the relation between diet, nutrition and the nervous system (central and peripheral, somatic and autonomic) in health and disease, research continues to examine the two-way interaction between nutrient intake and the function of the nervous system. The mechanisms of nutrient transport in the brain, the effects of malnutrition on central nervous system metabolism, and the neuroloogical pathways that control ingestive behavior are examples of the areas of research interest.

Priorities for research in this area include:

- o Studies to examine the dietary and metabolic factors that affect the two-way interaction between nutrient intake of precursors of neurotransmitters and the function of the central nervous system modulated by the neurotransmitters themselves.

- o Studies to consider the mechanisms of nutrient transport across the blood-brain and blood cerebrospinal fluid barriers as this influences the role of neurotransmitters in normal and abnormal brain metabolism.

- o Studies to investigate the electrophysiological activity of the brain resulting from changes in food intake in animals, as well as gustatory, olfactory and trigeminal stimulation.

- o Investigations to consider the neuroanatomical pathways connecting the gastrointestinal system to the hypothalamus and the effects of changes in the gastrointestinal system on electrophysical activity in the hypothalamus.

- o Studies to determine the neuroanatomical organizations and pathways of the somatic and autonomic nervous systems that control food intake and the behavioral, hormonal and metabolic mechanisms by which such pathways influence body weight.

- o Studies to examine the neurological mechanisms of taste and smell, and their common chemical reception and chemosensory stimuli in a variety of animal models.

- o Investigations to better define the effects of protein-calorie malnutrition on central nervous system metabolism.

- o Basic studies to investigate the effects of nutritional deprivation on the development of biochemical alterations linked to changes in higher cognitive functions of learning, memory, and psychosocial behavior throughout the entire span of life.

- o Studies to explore the relationship between vitamins (e.g., B_{12}, A, and C) and/or trace elements (copper and selenium) and the physio-

chemical functioning of the central nervous system, as well as the psychological higher functions of cognition and memory.

- o Studies on the effect of chemosensory dysfunction on the course of the natural history of dementias and other degenerative processes of the central nervous system (e.g., amyotrophic lateral sclerosis, multiple sclerosis, and myasthenia gravis).

- o Studies to better understand the role of the central nervous system in the etiology of obesity by examining the neurophysiology and neurochemistry of ingestive behavior, including appetite, feelings of hunger, satiety, eating, drinking, tasting, smelling, etc.

- o Studies of the abnormalities in the brain of genetically obese animals.

- o Studies of the relationship between obesity and stroke, i.e., whether obesity per se is a risk factor for stroke or is associated with other risk factors for this disease.

- o Studies to elucidate the intermediary mechanism modulating the effect of diet on atherosclerosis and its impact on the natural history of cerebrovascular disease.

- o Studies to explore the effects of central nervous system trauma on carbohydrate, fat and protein metabolism and to determine adequate dietary interventions needed to restore nutritional balance in order to minimize damage and accelerate recovery.

- o Studies on the use of high-fat diets in the treatment and control of seizures in children.

- o Studies on abnormalities in gastrointestinal absorption of hereditary sensory neuropathy.

- o Investigations to consider the relationship between dietary habits of various primitive cultures and the incidence of slow virus infections, such as Creutzfeldt-Jacob disease, Alzheimer's disease and amyotrophic lateral sclerosis.

- o Studies to consider the metabolic effects of nutrients on inborn errors of metabolism associated with neurological impairment.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Food Allergy

Allergic or hypersensitivity reactions to food are considered to be important triggers of classic allergic disorders, such as eczema and asthma in children. Other illnesses, such as behavioral and psychiatric disorders in both children and adults and rheumatoid arthritis, have also been attributed to adverse reactions to food. Unfortunately, owing to a lack of uniform and standard diagnostic tests there has been very little scientific data in support of many of these claims. Further research is needed to clarify the nature of allergy to cow's milk, to examine the manifestations of behavioral changes and other clinical abnormalities in response to food, and to assess the value of skin and antibody assays for the diagnosis of food-induced reactions.

Priorities for research in this area include:

- o Basic studies to examine the mechanisms of absorption of food substances and antigens across intestinal barriers in newborns in order to clarify the nature of cow's milk allergy and thereby develop improved methods of diagnosis.

- o Studies to explore the possible relationships between adverse reactions to food and behavioral changes such as hyperkinesis in children, depression, insomnia, tension headache, and schizophrenia.

- o Investigations to determine the mechanisms by which certain foods or food substances trigger clinical abnormalities.

- o Collaborative studies to examine and compare individuals who supposedly experience allergic reactions to shellfish and peanuts with those who suffer with eczema, asthma, allergic rhinitis, rheumatoid arthritis and rheumatologic disorders in order to determine the value of skin tests and antibody assays for the diagnosis of food-induced reactions.

Nutrition, Infection & Immunity

Malnutrition is the most common cause of immunodeficiency in the world. Vitamin and mineral deficiencies, as well as protein calorie malnutrition, depress the immune responses of man. Undernutrition is a widespread and serious problem in the pediatric population in the less developed countries of the world, as well as in the hospitalized patients in the industrialized countries. The enormous public health concerns generated by the interaction of malnutrition and infection in the tropical environment and in American hospitals remains a focus of study.

Priorities for research in this area include:

- Studies to define the role of specific nutrients, such as zinc, iron, and vitamins A, E, and C, on white blood cells, bone marrow and reticuloendothelial immune function in vitro, in experimental animals, and in man.

- Studies to examine the modulating effect of defined fatty acid and lipid diets on immunity, including evaluation of their effect on prostaglandins and leukotrienes.

- Studies to better characterize the role of iron and other single nutrients in the enhancement of parasitic and bacterial virulence in order that new methods can be developed which interfere with the binding and metabolism of single nutrients by such pathogens.

- Studies to compare the effect of biological response modifiers in both well nourished and malnourished immuno-incompetent hosts.

- Studies to demonstrate the effects of parasitic and enteric infections on growth, well-being, and physical fitness.

- Studies to better characterize the mechanisms by which human milk modulates infections and allergies in infants.

- Studies to develop and test more powerful oral rehydration solutions, such as those containing casein and glycine and to examine their effects on malabsorption, dehydration and growth after infectious diarrheas in infants and children.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Nutrition and Trauma

Patients suffering from trauma and burns have serious physiological and metabolic demands that must be met for survival. Such patients are prone to infections, suffer a great deal of pain, and may be permanently disabled unless appropriately treated. Research related to trauma and burns is directed to the discovery of better ways to prevent death from injury, mitigate pain, speed recovery of patients and lessen the extent of disabilities caused by injury through proper nutrition.

Priorities for research in this area include:

- o Investigations to establish the nutritional requirements of burn and trauma patients.
- o Studies to examine the status of the patient's host defense mechanisms, his metabolic response, and his ability to respond to injury.
- o Studies on the nutritional requirements of convalescing victims and rehabilitation of injured patients.
- o Basic studies to examine the relationship between the metabolites of arachidonic acid which appears following severe injury and the nutritional status of the patient.

Total Parenteral and Enteral Nutrition

Research studies in the area of trauma and burns have found that optimal metabolic management does influence patient outcome. It is known that increased blood glucose commonly occurs following injury and this elevation is generally related to the severity of the injury. This tendency and the prolonged glucose tolerance curves have resulted in the use of such terms as traumatic diabetes and diabetes of injury which suggest insulin deficiency. More recently, it has been shown that there is increased glucose production and increased flow of glucose with adequate insulin response following injury. In addition to the altered glucose kinetics, there exists a sustained hypermetabolism and negative nitrogen balance which causes marked weight loss if a vigorous feeding program is not initiated.

Research priorities include:

- o Studies to examine the underlying mechanisms of the above changes.
- o Studies on the effectiveness of total parenteral nutrition on the survival of patients suffering from trauma and burns.
- o Studies to develop the appropriate nutritional support formula to avoid pulmonary edema and increase carbon dioxide production in burn patients.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Nutrition and Reproduction

Research in the area of nutrition and reproduction is of global relevance, particularly in the many less affluent nations of the world where nutrition and dietary habits have been shown to influence fertility.

Priorities for research in this area include:

- Studies to better understand the involvement of nutritional factors such as vitamins and minerals in reproductive processes, the reproductive consequences of low-protein diets, and the relationship of food resources to reproduction.

Maternal Fetal Nutrition

The nutritional status of the mother affects the mother and development of her child as well as her own health and well-being. Research must continue to elucidate the complex relationships between the mother and her fetus and the means by which nutrients pass from one to the other. Any interference with the delivery of the nutrients to the fetus or the inability of the fetus to adapt to physiological changes that occur during pregnancy due to congenital defects and chromosomal abnormalities result in fetal malnutrition.

Priorities for research in this area include:

- Studies to better understand the complex relationship between the mother and her fetus and the means by which nutrients pass from one to the other.

- Investigations to determine the effects of dietary elements such as iron, zinc, chromium, and copper during pregnancy on maternal nutrition and function and on total growth and development of the fetus.

- Studies to determine the nutritional requirements of pregnant women with metabolic disorders such as obesity, diabetes mellitus, hypertension, or inborn errors of metabolism.

- Studies to identify the fetus predisposed to intrauterine growth retardation in order that improved procedures for treatment in utero can be developed.

- Studies to determine the effect of maternal weight gain on fetal or neonatal status.

- Studies to identify nutritional factors that affect perinatal mortality and morbidity.

Infant, Child, and Adolescent Nutrition

Studies to examine the role of nutrition in the growth and development of infants and children constitute an important and active area of investigation. Continuation of such research will better define the nutrient requirements of the low birth weight infant, the normal full-term newborn, and infants during the first year of life. The effects of human milk and commercially prepared formula on optimal infant development will continue to be investigated.

Adolescence is a time of profound physical transformation; growth rates achieved during adolescence are exceeded only by those attained during fetal life and early infancy. The NICHD program of adolescent nutrition emphasizes the adolescent growth spurt, physical fitness, obesity, the special needs of the pregnant adolescent, as well as the increased nutrient demands caused by the growth spurt and the onset of puberty.

Priorities for research in this area include:

- Investigations to determine the nutrient requirements of normal, premature, and growth-retarded infants and to analyze the influence of human milk and synthetic formula on optimal infant development.

- Studies to determine the effects of parenteral and enternal nutrition on gastrointestinal development and function and on long-term behavioral and functional outcomes.

- Studies to examine the effects of human milk and commercial formulas on the growth and health of low birth weight infants and to identify the non-nutritional components of human milk and determine their function and mechanism of action, e.g., growth factors, antimicrobial factors, lipases and other enzymes.

- Studies to better understand: (1) the role of nutrition as a potentiating factor in brain development; (2) the effect of nutritional deficits and excesses in physical growth and maturation; and (3) the effects of non-nutritional food components on growth development and health of children.

- Studies to evaluate the growth rate for optimal physical and functional development.

- Studies to identify the effects of chronic and systemic diseases, nutrient imbalances, and/or hunger on physical growth and mental or motor development.

- Studies to identify the augmented nutritional requirements of the growth spurt.

- Studies to determine the nutritional needs of pregnant adolescents.

- Studies to establish the psychosocial-cultural determinants of adolescent eating disorders.

- Studies to identify factors that determine food selection and eating habits during adolescence, with particular reference to adolescent obesity, consumption of large quantities of food with low nutritional value, and stringent food faddism.

- Studies to identify nutrition antecedents of adult diseases through examinations of the development of obesity, insulin resistance, and glucose intolerance in infants, children, and adolescents, in order to supply the scientific basis for various kinds of intervention.

Nutritional Aspects of Gastrointestinal Development

Priorities for research in this area include:

- Studies to better understand the processes of cellular and tissue development in the gastrointestinal tract and how these relate to function.

- Investigations to further define the nature of digestive and absorptive disorders in infants, children, and adolescents in order to develop methods for their further nutritional management.

- Studies on the development of new methodologies in basic research needed to advance the field.

- Studies to increase efforts to stimulate basic studies on the processes of cellular proliferation, differentiation, and migration as well as increase research on the immune function of the developing intestine.

- Studies on the distribution of digestive capabilities among populations including studies on the distribution of intestinal enzyme activity among individuals and the relationship of the distribution to long-term food exposure.

- Further studies on the roles played by colostrum, human milk formulas, and weaning foods as stimulators of gastrointestinal development and function.

Dietary Therapy of Inborn Errors of Metabolism

The study of genetic variants in man and animal models helps to advance our understanding of both normal and abnormal biochemistry. Research on nutrition and genetics includes studies on inborn errors of metabolism, metabolic differences in nutrient requirements, chromosomal aberrations and determinations of cellular function, especially DNA repair mechanisms, and the effects of dietary intervention on inherited diseases or conditions. The nutritional management of the inborn errors of metabolism is a vast and important area of research that covers phenylketonuria, galactosemia, maple syrup urine disease, urea cycle enzyme deficiencies, cystinosis, Menkes' kinky hair syndrome, and the hyperlipidemias.

It is not yet certain how aberrant levels of nutrient substrates and their derivatives cause abnormal cerebral development in some infants or why the same dietary treatment often causes different reactions. The possible role of genetics and nutrition in the development of cancer, obesity, diabetes and coronary heart disease also needs further examination. New methods to help in the diagnosis of the various genetic variants in the population need to be developed in order to help prevent or ameliorate the manifestation of these diseases and conditions.

Priorities for research in this area include:

- o Investigations to assess the effect of diet on inborn errors of metabolism and to develop dietary therapy amenable to nutritional management.

Assessment of Nutritional Status

Research on nutritional status assessment includes investigations to develop and evaluate various methods of determining the consumption of nutrients throughout the life cycle, from fetal life to infancy, childhood and adolescence.

Priorities for research in this area include:

- o Studies to develop new methods to assess nutritional status, focusing on methodologies that are noninvasive and pose the least possible risk to the individual while being both precise and convenient.

- o Studies to identify markers of nutritional status as related to pregnancy and lactation, postpartum or post-lactation physiological adjustments, the first year of life, and adolescent growth spurt.

Cultural and Behavioral Aspects of Nutrition

The motivating forces controlling food selection and food intake are diverse. The physiological factors of taste, smell, and gastric and humoral responses to certain foods are often influenced by social, cultural and religious values, as well as learned habitual behaviors. Studies are needed to attempt to define the exact role of these values and behaviors on food preferences and aversions, as well as to define the influence of dietary intake on subsequent behavior.

Priorities for research in this area include:

- o Studies to better understand the influence of nutritional individuality and cultural and behavioral factors on diet, taste development, food avoidances, and food preferences.

- o Studies to determine the impact of environmental variables on nutrient requirements.

- o Studies to identify the cultural and behavioral determinants of choice and duration of infant feeding practices.

NATIONAL EYE INSTITUTE

Nutrition and Eye Diseases

Malnutrition, particularly vitamin A deficiency, is a leading cause of childhood blindness and impaired vision in developing nations throughout the world. Nutrition-related eye problems also exist in developed countries. These include the complicating side effects of some prescribed medications which interfere with normal vitamin metabolism and several inherited or acquired diseases which interfere with the absorption and/or metabolism of individual vitamins. A considerable amount of research is concerned with studying the normal metabolism of ocular tissues, particularly the role of vitamin A and other nutrients in normal retinal and corneal function and the effects of experimental malnutrition with particular emphasis on deficiencies of protein, amino acids, and certain vitamins and minerals. Possible nutritional risk factors for the development of cataracts are under investigation both in the laboratory and among human populations. The effects of nutrients on the metabolic processes involved in immune responses and the impact of nutritional status on the expression of developmental hereditary disorders of the retina and the choroid are also being explored.

Priorities for research in this area include:

- Studies to determine visual function and biochemical responsiveness to diets low in arginine or vitamin B_6, or low in both, among patients with inherited retinal degeneration, i.e., gyrate atrophy.

- Investigations to determine the mechanism by which taurine deficiency leads to irreversible photoreceptor malfunction or death.

- Examinations of vitamin E's role in the hereditary retinal diseases in which lipofuscin-like material has been noted in high concentrations in the pigment epithelium.

- Studies to examine the special aspects of the retinal pigment epithelium (RPE) transport and metabolism of micronutrients, nucleotides, hormones, and other cell products in controlling the properties and the functions of the RPE.

- Studies of the dietary levels of vitamins E and A, selenium, zinc, xanthophyll or taurine that will optimally maintain photoreceptors and minimize macular degeneration.

- Studies of the optimal range of dietary intake of micronutrients to maintain optimal visual function for older people, including those with aging-related maculopathy.

- Studies to consider environmental, nutritional, and other factors that may affect the quality of photoreceptor function and the rate of photoreceptor degeneration and aging.

- Studies of the relationship of vitamin A deficiency to generalized protein calorie malnutrition in the etiology of corneal disease, and the possible benefits of vitamin A therapy in maintaining ocular surface epithelium.

- Studies to determine the role of the inner corneal epithelium in the nutrition and hydration of the outer epithelium and other corneal cells.

- Studies to determine the nutritional and substrate requirement of the corneal endothelium.

- Studies to examine the roles which vitamin A and ascorbate play in the prevention and treatment of corneal ulcers and in the secretion of the enzyme collagenase and its subsequent degradation of proteoglycans.

- Investigations to consider the interactions among nutrition, disease, and the environment as risk factors in the development of cataracts of varied etiologies.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Nutrient Toxicities and Food-Borne Contaminants

Advances in food technology during the last century have improved the availability and general nutritional quality of our food supply, but extensive replacement of conventional unprocessed foods with highly processed or fabricated foods may result in insufficient or unbalanced intake of some nutrients. Processing may also result in food components that are more easily or less easily utilized by the body, or convert food components into compounds that are potentially toxic. However, it is essential that the nutritional quality of our food supply does not deteriorate.

Research is directed toward understanding the effects of food-borne contaminants and food additives on the biological system. Examples of these research efforts are studies on the metabolism and carcinogenicity of aflatoxins; selenium toxicity and metabolic significance of selenium; intestinal absorption and distribution of heavy metals; and heavy metal toxicity. NIEHS plans to continue support of these or similar studies and to expand support of nutrition in an effort to elucidate the role of environmental agents in interacting with specific nutrients or other dietary components in the production of adverse health effects.

Priorities for research in this area include:

- o Investigations to examine the effects of altered diets on the toxic effects of chemicals.

- o Studies on general or specific agents or nutrients, singularly or in combination, that affect microsomal, mitochondrial or nuclear enzyme induction in specific organs or tissues. Species and strain differences will also be of importance when applied to laboratory mammalian animals.

- o Investigations to examine the nutritional factors responsible for enzyme activities of target or non-target organs in modifying toxicity of mutagens teratogens, or carcinogens.

- o Studies to determine how food preparation parameters may alter food constituents into mutagenic or otherwise toxic products.

- o Studies to develop animal models for human exposure to environmental toxicants to provide insight into the biochemical, physiologic and cellular events which occur intraluminally and within the tissues of the tract.

- o Studies to develop sensitive tests for detecting early damage to the human alimentary tract by environmental toxins.

NATIONAL INSTITUTE OF AGING

Nutrition of the Elderly

Nutrition research in relation to problems associated with age properly covers a wide range of topics and a large variety of methodologies. The experimental system may be human or nonhuman and involve any level of biological organization. At one end of the research spectrum are quite basic studies such as those aimed at determining the biochemistry of individual nutrients; at the other end are studies at the level of the whole organism. Since many of the problems and diseases of the elderly have their origins in earlier adult life, studies on the role which nutrition during earlier adult years plays in the development of the disease and problems of the elderly are as relevant as studies on the elderly themselves. It is only by integrating research results from a variety of experimental approaches and levels of analysis that an understanding of the complex role played by nutrition in the aging process and in the promotion and maintenance of health in the elderly will be derived.

Priorities for research in this area include:

- o The examination of the interactions between nutrition and the aging process in order to better understand the extent to which nutrition influences the decline in the physiological changes that occur as a function of age, and the extent to which age-related physiologic changes affect nutritional status of the elderly individual.

- o Studies to establish on a sound scientific basis the optimal nutrient intake of the elderly; at present, most recommendations are based on extrapolations from what is known of the nutrient needs of young adults. However, it is reasonable to expect that these needs will be modified by several conditions commonly associated with aging such as age-related physiologic changes, changes in the level of physical activity, and very significantly, chronic drug use.

- o Investigations to validate the nutritional status assessment methodology used for other age groups as appropriate for the elderly and to determine norms. For example, if a lower level of a specific nutrient is found in elderly populations, it is important to determine whether that level is due to a physiologic change in the set-point for that nutrient or prolonged undernutrition, whether a specific supplement will alter the level of the nutrient in question, and if there is any benefit in terms of health or longevity from such supplementation? In addition, correlation of nutritional status with subsequent morbidity and mortality can provide useful information concerning the contribution of long-term nutritional status to the etiology and pathogenesis of diseases prevalent in the elderly (e.g., osteoporosis, hypertension, arteriosclerosis, various anemias, gallstones, and certain forms of senile dementia).

- o Investigations to identify dietary patterns which may make certain subsets of the elderly population especially vulnerable to malnutrition and to examine the processes contributing to the specific

dietary patterns, for example, changes in taste and smell, in salivary secretion, or in dentition.

- Studies to consider the role which nutrition plays in longevity since in several animal species prolonged food restriction results in an increase in life span. Although the mechanisms responsible for the increase are not yet known, this increased life span is associated with a delay in the onset and progression of specific diseases. However, laboratory animals may actually be kept in a state of chronic overnutrition vis-a-vis the wild state. Thus, it may not be food restriction, but rather the lack of food excess which is associated with an increased life span. Studies need to examine the type of "restriction" which is effective, the biological mechanisms involved, and how these observations in several other species are related to man.

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